Institute for Health and Consumer Protection

European Chemicals Bureau

NOTIFICATION OF NEW CHEMICAL SUBSTANCES IN ACCORDANCE WITH DIRECTIVE 67/548/EEC ON THE CLASSIFICATION, PACKAGING AND LABELLING OF DANGEROUS SUBSTANCES

TECHNICAL GUIDANCE FOR THE COMPLETION OF A SUMMARY NOTIFICATION DOSSIER FOR A NEW CHEMICAL SUBSTANCE UTILISIN THE STRUCTURED NOTIFICATION INTERCHANGE FORMAT (SNIF) BASE-SET AND LEVELS 1 AND 2

EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

2002

EUR 20542 EN

LEGAL NOTICE

A great deal of additional information on the
European Union is available on the Internet.
It can be accessed through the Europa server
(http://europa.eu.int)

EUR 20542 EN

Printed in Italy

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Ispra, November 2002

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TECHNICAL GUIDANCE FOR THE COMPLETION OF A SUMMARY NOTIFICATION DOSSIER FOR A NEW CHEMICAL SUBSTANCE UTILISING THE STRUCTURED NOTIFICATION INTERCHANGE FORMAT (SNIF)

This document has been prepared by the Competent Authorities of the EU Member States for the implementation of Directive 67/548/EEC as guidance for those preparing the notification of a new chemical substance in accordance with EU Directive 67/548/EEC, as amended for the seventh time by EU Directive 92/32/EEC (ref.: O.J. L 154, 5 June 1992). Prospective notifiers of a new substance are advised to always contact the Competent Authority (CA) in the appropriate country before starting work on preparing a notification dossier. Any questions resulting from this guidance should be addressed to the relevant CA. This document primarily addresses the completion of the summary notification dossier; questions on other aspects of the Directive should again be addressed to the relevant CA.

This text has no legal value. The requirements in EU Directive 67/548/EEC are paramount and take precedence over this guidance.

GENERAL INTRODUCTION:

1. TECHNICAL DOSSIER TO BE SUBMITTED

This is a guidance note for completing a standardised summary form for the notification of a new chemical substance in quantities of > 10 kg per annum in the European Union, Norway, Iceland and Liechtenstein (known collectively as the European Economic Area (EEA)) according to Annex VII A, B, C, or D, or Annex VIII of Directive 67/548/EEC. The summary form will be a part of the technical dossier required for the notification of a new substance. In addition to the summary form the technical dossier should include all test reports, the chemical structure, spectra, a proposal for a material safety data sheet in the event that the notified substance should be classified and labelled, and possibly a draft risk assessment. Any risk assessment should follow the principles contained in Directive 93/67/EEC. Notifiers should consult the relevant national authorities for specific requirements on language to be used and the number of copies of the notification dossier to be provided. All CAs prefer the summary to be submitted on an electronic format (see item 4 of the General Introduction); in some countries this is a legal requirement.

In general, the potential for exposure to a notified substance is related to the quantity on the market. Therefore, as the supply level and potential for exposure increase, the potential for adverse effects also increases. Consequently there is a need to obtain more information on hazards of the substance, and hence the tonnage-related testing requirements of Directive 67/548/EEC (known as the Dangerous Substances Directive). The levels of supply at which further testing may either be requested or become necessary are described in Article 7(2) of **Directive 92/32/EEC** (the seventh amendment to Directive 67/548/EEC).

The following categories are defined (in **Directive 92/32/EEC**):

- a reduced notification according to Annex VII C of the Directive for substances marketed in quantities between 10 and 100 kg per year per manufacturer (or < 500 kg cumulatively);

- a reduced notification according to Annex VII B of the Directive for substances marketed in quantities between 100 and 1000 kg per year per manufacturer (or < 5000 kg cumulatively);

- a base set notification according to Annex VII A of the Directive for substances marketed in quantities equal or more than 1000 kg per year per manufacturer (or > 5 tonnes cumulatively).

An overview of the relevant sections to be completed for a notification according to one of these categories is given in Annex 1 to this guidance.

The general requirements for further testing at specified higher levels of supply are set out in Annex VIII of Directive 67/548/EEC, the latest update of which is contained in Annex VIII of **Directive 92/32/EEC.** Nevertheless, tests in addition to those specified in Annex VIII can be requested, or submitted for assessment.

2. TEST METHODS AND TESTING STRATEGIES

Approved test methods, to provide results which can permit further classification of notified substances, are described in **Directives 87/302/EEC, 92/69/EEC and 96/54/EEC**. However, most OECD test methods are equally acceptable, and in some circumstances, other validated and scientifically accepted methods can be used provided adequate justification is presented or, where there is no approved method for a particular objective.

A comprehensive guide on the testing strategies available to assist the progressive collection of information, in order to Conduct risk assessment of notified substances, is provided in the **'Technical Guidance Document in support of the Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and the Commission Regulation (EC) 1488/94 on the Risk Assessment for Existing Substances (known as the 'Technical Guidance')'**. This has been published by the Office of Official Publications of the European Communities EC catalogue numbers CR-48-96-001-EN-C, CR-48-96-002-EN-C, CR-48-96-003-EN-C, CR-48-96-004-EN-C. It is recommended that Competent Authorities and Notifiers refer to this guidance in the interest of promoting standardisation of hazard identification and risk assessment procedures. This document has been published in four parts (the EC catalogue numbers are CR-48-96-001-EN-C, CR-48-96-002-EN-C, CR-48-96-003-EN-C, CR-48-96-004-EN-C).

3. ADDITIONAL TESTING POST-BASE SET AND AT LEVEL 1 AND LEVEL 2

POST-BASE SET

It is important to note that one of the outcomes of the environmental risk characterisation carried out at the Base Set in accordance with Directive 93/67/EEC, may indicate the need to carry out certain Level 1 studies immediately, rather than wait for the tonnage trigger to be reached.

LEVEL I

Article 7(2) of Directive 92/32/EEC may require additional (eco)toxicity testing when the tonnage placed on the market reaches 10 tonnes per annum or 50 tonnes total; the tests which may be required are listed in Annex VIII. When the tonnage reaches 100 tonnes per annum or

500 tonnes in total, all the tests listed in Annex VIII will normally be required. There may be technical reasons why a particular study cannot be performed, for example if it is not appropriate or an alternative study is preferable. In these cases it is for the notifier to provide the competent authority with full justification for any deviations from the requirements.

LEVEL II

Article 7(2) of Directive 92/32/EEC also makes provision for further testing when the quantity placed on the market reaches 1000 tonnes per annum or 5000 tonnes in total. The testing programme is outlined in Annex VIII and reflects the possible need for further information. This information maybe necessary in the light of the results obtained from testing at the Base Set and Level 1.

4. SNIF PROFORMAS

The Structured Notification Interchange Format (SNIF) is the computer-based system for the exchange of essential notification information, adopted throughout the European Union (EU) in June 1992. The Competent Authority should be contacted to obtain the required SNIF software.

This guidance is intended to help standardise the format, quality and consistency of data collection in SNIF for studies conducted at base set level and at higher levels of supply.

In the following text, the index numbers for the studies and the format for collection of information, conform to the style of those in the SNIF software application, which is based on the Summary Notification Dossier (SND) document XI/85/90 (available from the relevant CA). Data may be viewed or edited online, using the SNIF software, or offline, using a printout of the SNIF information.

The procedures described below are intended to satisfy either approach, since edits collected on paper must ultimately be transferred back into the software application.

In some cases, e.g. mutagenicity testing, a single proforma is utilised for several test methods. For others, the proforma is designed specifically for an individual test method. There is also a draft proforma for ‘Other tests' (index 4.7), which is intended to be flexible and to permit data collection for additional tests.

In entering data to the proformas, all descriptions of toxic signs, observations and general comments should be as clear, concise and precise as possible. Also, in addition to entries of positive toxic effect, entries of 'no toxic effect', or, where appropriate, 'not examined' should be included to maintain a complete and consistent record. Nevertheless, in the SNIF software application, no entries are obligatory (this includes tabular entries). However, if any field is left blank an entry may be necessary under **‘Comments'** to explain why.

Under **Method,** care should be taken to make clear if a test method is in 96/54/EEC, 92/69/EEC, 87/302/EEC, OECD test methods, or from a published paper.

Under **Body responsible for test,** entries must be in the recognised format. SNIF contains a pre-defined list of Test Facilities together with selection codes for entry of this information.

Under **Comments** it is important to note if a study is unacceptable and to indicate why. Also, scientific justification should be available for any deviation from an approved test method, or to support a non-standard specialised test method.

Additionally, classification and labelling (C&L) recommendations are normally not included in **Comments,** except in circumstances that require clarification, e.g. R48 is justified, as there is a need to indicate whether Harmful (Xn) or Toxic (T) is appropriate for the label; whereas R61 is not justified as it indicates significant toxic effects observed in the dams.

In the guidance below, the standard proforma is represented in **bold text,** and guidance on responses is represented in normal text. Fields normally required, at levels 1 and 2 are given in *italics*.

Comment on SNIF proformas

The proformas presented in the guidance below are those currently in existence in the SNIF software. It is nevertheless important to note that some of these proformas are not adequate for complete data collection in a common format. In many circumstances it is, therefore, necessary to include additional information in the 'Comments' section.

In view of this, it is expected that as the use of SNIF proformas increases, they will be updated where necessary to make them more user friendly, e.g. important information will be prompted for and therefore be less likely to be overlooked.

Contact the Competent Authority for obtaining the most recent version of the SNIF.

5. CONSULTATION OF THE COMPETENT AUTHORITY BEFORE CARRYING OUT ANIMAL TESTING

Before carrying out animal testing, for the purpose of collecting test data for the notification of a new substance, the potential notifier must enquire of the Competent Authority as to whether the substance has already been notified and, if so, the name and the address of the first notifier. Enquiries should be made, in the first instance, to the Competent Authority where the notification is to be made. In order to ensure that the enquiry is genuine and not simply a competitor trying to identify the name or interests of other suppliers, the enquirer must provide the following information:

1. Name, address and contact person of the potential notifier if enquiry is via a third party (for guidance see notes to section 0.2.10, page 6 of this guidance).
2. Name and address of the manufacturer (for guidance see notes to section 0.2.20).
3. IUPAC name or description if a UVCB substance (for guidance see notes to section 1.3.10.10/20).
4. CAS number (for guidance see notes to section 1.3.10.30/40).
5. Empirical and structural formula; stereochemistry for optical geometric isomers (for guidance see notes to section 1.3.10.50/60).
6. Nature and percentage of impurities and additives (for guidance see notes to section 1.3.20/40).
7. EEC number of substance, if believed to be on ELINCS.
8. Analytical and spectroscopic data (for guidance see notes to section 1.3.00 of the summary).
9. Intended use (for guidance see notes to section 2.1.00 of the summary).

The key items are the analytical and spectral data and intended use. These demonstrate that the enquirer has taken time to obtain a sample of the substance and identify a market for it. The other information follows from the former and is to aid the Competent Authority in ensuring that a

complete search of the records held is possible. It also confirms that the substance is sufficiently identical in terms of purity and impurities to that originally notified to allow the 'sharing of data'.

6. CONFIDENTIALITY

In conformity with Article 19.1. of Directive 92/32/EEC, notifiers may indicate which information in the notification dossier they wish to be treated as confidential. If confidentiality is requested for any item, justification must be given and the Competent Authority receiving the dossier will have the final decision on the confidentiality or otherwise of information in the dossier. If information is accepted as being confidential, it shall be kept secret by the Commission and the Member States as described in Article 19.2 of the Directive. However, it should be understood that Article 19.1 limits those items of information for which confidentiality can be claimed. In the summary dossier the notifier may request confidentiality by ticking the column, where it exists, alongside the information he wishes to be regarded as confidential.

The notifier should justify in the summary form, or in a separate annex, their claim to keep the indicated information confidential. The information given should be sufficient to evaluate the justification of the confidentiality claim. Possible confidential information can be divided into five main categories, namely:

- Chemical identity of the substance,
- Impurities,
- Uses and desired effects of the substance,
- Volumes on the market,
- Names of bodies responsible for the tests.

The justification for the claim for confidentiality should be given for each of these main categories, if appropriate, in a separate annex. When the summary has been provided in the SNIF format, the claims for confidentiality should be justified sufficiently, in a separate annex for each of the above mentioned main categories. When the information is claimed confidential without a sufficient explanation, the Competent Authority may decide that the claim for confidentiality is not justified.

7. APPLICATION FOR A PROCESS-ORIENTATED RESEARCH & DEVELOPMENT EXEMPTION

In conformity with Article 13.2 of Directive 92/32/EEC, substances solely intended to be used for process orientated research and development (R&D) purposes, with a limited number of registered customers, in quantities which are limited to that needed for process-orientated R&D, qualify for an exemption of one year. The notifier should justify the request for an exemption of one year by providing information on the research and development proposed (Annex 6 of this guidance contains a draft list of the sort of information that may be required. Notifiers should contact the Competent Authority who will detail the up-to-date information they require). A submission for the exemption is required in each Member State where supply is to occur.

Furthermore, the notifier should communicate to the Competent Authority in each Member State where supply is to occur any additional information. In addition notifiers should consult the national regulations of the relevant Member State(s) or contact the Competent Authorit(y)(ies) for national requirements.

On granting an exemption of one year, the substance must not exceed the quantity stated in the exemption and the deferred notification should normally be submitted at the end of the exemption period.

In exceptional circumstances the exemption may be extended for a second year provided that the notifier can demonstrate, to the satisfaction of the CAs, that such an extension is justified. Where possible this justification should be included in the original application for an R&D exemption.

8. GENERAL POINTS ON COMPLETING THE SUMMARY FORM

8.1 Tests should be carried out on the substance including any essential additives (for the stability of the substance) and impurities it normally contains, but excluding gross amounts of water, mineral oil or other solvents that are sometimes present in the substance eventually marketed. Ideally, one batch of substance should be used for all tests. If for any test the composition of the substance is different from that quoted in sections 1.3.10 to 1.3.40 then full details should be provided.

8.2 Where appropriate, details of the stability of the substance under storage conditions prior to testing and in any vehicle used during testing, should be specified in the relevant section(s) of the summary document. In particular, where the long-term stability is in doubt the composition must be checked (as in item 1.4.00) before testing.

8.3 Phrases such as (under 3.0.60) “insoluble in water” are discouraged. A limit test should be performed under such circumstances so that a positive response, such as "< 0.1 mg/l (analytical limit)", can be entered.

8.4 All tests should be conducted in accordance with Annex V methods (Directive 87/302/EEC, 92/69/EEC and 96/54/EEC). Exceptions to this should mainly be as a consequence of changes to OECD test guidelines or developments in the field of animal welfare. The entry under “Method” would normally, therefore, be Annex V (quoted as the Directive number). If a test has been performed that deviates from Annex V/OECD, or if a required test has not been performed, the nature of the differences must be indicated under “Method” and justification for the deviation or the omission, acceptable to the Competent Authority, must be provided under “Comments”.

8.5 All testing must be performed in accordance with the principles of Good Laboratory Practice (GLP) (Directive 87/18/EEC, Official Journal of the European Communities, 17 January 1987, L 15, p29). Test reports should contain suitable signed GLP and Quality assurance (QA) statements.

8.6 Labelling proposals should be for the substance as tested and not preparations and should be entered at Section C. Criteria for labelling are given in Directive 93/21/EEC as published in the Official Journal of the European Communities, 4 May 1993, L110.

8.7 Notifiers are encouraged to consult the relevant Competent Authority in the Member State in which they intend to notify if they have any queries (e.g. on test protocols).

8.8. In this guidance the sections related to the additional test data that may be required for level 1 and level 2 are presented in 'Italics'. These sections can be ignored for the base-set notification.

DETAILED COMMENTS ON COMPLETING THE SUMMARY DOSSIER

SECTION 0 DETAILS OF THE NOTIFICATION

Most of the information requested in section 0 must not be completed by the notifier. It is clearly indicated which sections are relevant for the notifier to complete.

0.1.00 DETAILS OF THE NOTIFICATION

0.1.10 General information

Full dossier

Indicate whether the notification is the first notification of the substance for which a full base set must be provided, or the notification refers to a previous submitted notification for which only section 0 suffice to complete.

There are several cases for which completing only section 0 is not sufficient:

- In the case of only a previous notification under the 6th Amendment also the relevant sections with additional information required under the 7th Amendment must be provided.
- When a repeated notification refers to a previous submitted notification at lower level, the relevant sections related to the required additional information must be completed.

Member state of notification

Date of notification

Only to be completed by the Competent Authority

Lead dossier

Previous notification numbers

Name of the substance (Trade name or other identification name)

The notifier should indicate clearly the names to appear in the European List of Notified Chemical Substances (ELINCS).

0.2.00 DETAILS OF THE NOTIFIER AND THE MANUFACTURER

0.2.10 Notifier

Give the name and address of the notifier, and the name of the contact person responsible for the notification. Indicate whether the notifier is the domestic manufacturer, an importer of the substance manufactured outside the EEA, or a sole representative for the notification of the substances manufactured outside the EEA. In the case of the importer or the sole representative, complete section 0.2.20

0.2.20 Manufacturer (in the case of import of the substance)

When the notifier is an importer or a sole representative, give in this section the name(s) and address(es) of the manufacturer(s) outside the EEA, and the name(s) of the contact person(s). In the case of more than one manufacturer, the notifier must provide information to show that the chemical identities of the substances produced by the manufacturers do not deviate from the chemical identity of the substance to be notified.

Importer(s) for the sole representative

When the notifier is a sole representative complete this section.

0.3.00 NAME TO BE INCLUDED IN ELINCS

To be completed by the notifier (see section 0.1.10).

0.3.10 View of the authority with regard to the publication

To be completed by the competent authority.

0.3.20 ELINCS chemical name

To be completed by the European Chemicals Bureau.

0.3.30 EEC number

To be completed by the European Chemicals Bureau.

0.4.00 CLASSIFICATION AND LABELLING

To be completed by the Competent Authority. This section gives the view of the Competent Authority with regard to the classification and labelling of the substance.

0.4.10 Classification

0.4.20 Labelling

0.5.00 COMMENTS OF THE COMPETENT AUTHORITY

To be completed by the Competent Authority. The Competent Authority gives in this section its comments and observations with regard to the information provided in the notification including the acceptance, and comments on the proposal by the notifier for the classification and labelling. Technical details related to specific tests must be given in the "Comments" sections of the respective test. Errors or misinterpretations in the results might be noted in this section, but must be corrected as much as possible in the respective sections.

0.6.00 COMMENTS OF THE COMMISSION

To be completed by the European Chemicals Bureau.

SECTION A TECHNICAL DOSSIER

SECTION A1 IDENTITY OF THE SUBSTANCE

1.1.00 NAME

1.1.05.10 Mixture

Indicate whether the substance is a mixture or a substance as such. Detailed information of the composition must be given in section 1.3.

Name in the IUPAC nomenclature

Notifiers should be aware that where the Directive requires the disclosure of the chemical name for the purpose either of publication in ELINCS (the European List of New Chemical Substances, see Commission decision of 21 December 1984, published in the Official Journal on 2 February 1985, No L 30, page 33) or, in Annex 1, it is the information given in this section which will be used in determining how the substance will be described.

1.1.05.20 Trade name(s):

Include all trade names and/or other public identifiers under which the substance will be marketed in the EEA. For dyestuffs, the Colour Index Name will suffice if the substance will be marketed under this name alone. Whether a formal registered trade name or, in its absence, simply an identifier, in the eventual summary this item will be entered under the title “Trade Name(s)”.

1.1.05.30 Other names

E.g. company code number or internal name.

1.1.05.40 CAS-number (in the case of a mixture)

If available. If not yet allocated leave blank or enter NYA.

1.1.05.50 Degree of purity

Give the typical percentage purity with the upper and lower limit for typical commercial batches of the substances. If the substance is a complex reaction mixture, give the typical percentage purity with upper and lower limits for each of the main components.

1.3.00 COMPOSITION OF THE SUBSTANCE (GENERAL)

The information given in this section should be for typical batches of the substance. It is recognized that notified substances will inevitably include some impurities (see section 1.3.20) and if necessary some essential additives (see section 1.3.40). However, the substance tested should not include gross amounts of separable solvents nor substances added subsequently to make a preparation.

1.3.10 Component(s)

1.3.10.10/20 IUPAC-name(s)

Give the IUPAC-name in the national language and in English of the component(s).

1.3.10.30/40 CAS-number/name

Give the CAS-number(s) and the name according to the CAS-nomenclature of the component(s), if available, otherwise leave blank or enter NYA.

1.3.10.50/60 Empirical (molecular) and structural formula(e) of the components

Strictly the molecular formula - and should be given according to the (traditional) Hill system and also according to the CAS system, where this differs from the Hill system formula. For UVCB compounds/products by process, an empirical formula should be determined. In the case of a mixture, strictly the molecular formulae for each component can be given or used to explain the structure given (e.g. variation in counter-ions, possibility of isomers etc.).

Comment, if no structural formula can be given.

1.3.10.70 Molecular weight of the substance

Give the molecular weight of the notified substance

1.3.10.100 File name

When the structural formula has been prepared by using sophisticated software capable to export a MOL-file (e.g. ISIS and CHEM-X) the structure might be submitted on diskette. Give in this section the name of the MOL-file on diskette. This is not currently in use.

1.3.10.110 Smiles code

If available, give the structural name according to the SMILES-notation.

1.3.10.120/130 Polymer identity

Both the average molecular weight (Mn) and the molecular weight distribution must be provided. These can be determined using GPC. Distribution curves must be provided in the form of a table, or as a figure (differential frequency or sum percentage against log M).

1.3.10.140 Typical concentration of the component(s)

Give the percentage of the component(s). Indicate whether by weight (preferred) or volume giving values for the substance tested and, where possible, the expected commercial range.

Note: Composition of the used test batches of the substance(s) must be provided in section 2.6.

Give the typical percentage purity with the upper and lower limit for typical commercial batches of the substances. If the substance is a complex reaction mixture, give the typical percentage purity with upper and lower limits for each of the main components.

1.3.20 Identity and percentage of impurities

Give the IUPAC-name(s), nature, CAS-numbers, if available, and percentage of the main impurities including isomers and by-products and the total number of unidentified impurities. NR minor or, even trace, impurities should be included if they have, or if they may reasonably be suspected to have, toxicological importance; and for labile substances the nature of resulting degradation products should also be stated. Indicate whether by weight (preferred) or volume giving values for the substance tested and, where possible, the expected commercial range (as for 1.3.10.).

Note: Composition of the used test batches of the substance(s) must be provided in section 1.5.

Provide the following information (1.3.30, 1.3.32 and 1.3.33) on paper, as they are not present in the SNIF proforma.

1.3.30 Polymer starting materials and end groups

Give the identity and percentage of starting monomers and substances, which will be tied in the polymer material, IUPAC-name, and CAS-number if available

1.3.32 End groups and reactive groups

IUPAC-name, CAS-number if available and frequency of end (reactive) group(s)

(number/repeating unit)

1.3.33 Identity of monomers not reacted

IUPAC-name, CAS-number if available and percentage by weight (preferred) or volume giving values.

1.3.40 Essential Additives

Give the IUPAC-name(s), nature, function, CAS-number(s), if available, and approximate amount (percentage or ppm) of any stabilizing agent, inhibitor or other essential additive required for the stability [isolation] of the substance, but exclude substances added subsequently to make a formulation or a preparation.

1.3.50 Spectral Data

Indicate which have been measured in order to confirm the structure given, noting significant wavelength or other data here and attaching annexes as appropriate. Give solvent used and/or other essential details as indicated. Clear copies (rather than originals) with scales properly marked and for 1H NMR spectra (see under c) the integration curve should be provided; concentrations used should ensure the most intense substance-related peaks approach the full-scale mark; the intensity of weak NMR peaks should be increased vertically and complex pattern expanded. For each type of spectrum the following information should be indicated on the spectrum itself.

a) UV/Visible spectrum
   The identity of the substance; solvent/concentration; range; position (and epsilon value) of main peaks; effect of acid; effect of alkali.

b) IR spectrum
   The identity of the substance; medium; range; results.

c) NMR spectrum
   The identity of the substance; nucleus/frequency; solvent and as appropriate internal or external reference; result (indicate the signals corresponding to the solvent and the impurities).

d) Mass Spectrum
   The identity of the substance; accelerating voltage; method of loading (direct insertion via GC, etc); mode (Electron Impact, Chemical Ionisation, Field Desorption, etc); molecular ion (M); significant fragments (i.e. especially those at higher mass); M/Z values or assignments.

e) Gel permeation chromatography (only for polymers)
   The identity of the substance; solvent; temperature; characteristic values of the standards and columns; separation efficiency.

f) Other spectra

1.3.61 Chromatography

Do not complete. Method should be given at section 1.4 and an HPLC etc. trace included in the analytical report.

1.4.00 METHODS OF DETECTION AND DETERMINATION

A brief description of the methods used to support the information given under section 1.3.10/1.3.30, or the appropriate bibliographical references, should be given. The description and/or the appropriate bibliographical references should be sufficient to allow a competent analytical chemist to repeat the measurements without further aid (e.g. for gas chromatography, give column dimensions and construction, packing material including support, any special treatments given, temperature used, internal standard if applicable, detectors, etc. where spectra have been used, simply refer to the details under section 1.3.50.

1.5.00 COMPOSITION ON THE TESTED SUBSTANCE

Give the exact composition of the samples, and the corresponding batch numbers, which were used to perform the tests in the sections 3.0.1 to 5.6.00 (the purity etc. must be within the ranges given in sections 1.3.10-1.3.40).

It is much preferred that all tests are conducted on the same batch and, if so, this should be clearly indicated under this section.

SECTION A2 INFORMATION ON THE SUBSTANCE

2.0.00 INFORMATION ON THE SUBSTANCE

2.0.10 Technological process(es) used in production

Only applies to sites in the EEA. A brief description of all technological process(es) used in production including specification of the system in which the notified substance will be produced (open/closed, continuous/batchwise), duration and frequency of production, maximum capacity per time-unit, pressure and temperature during processing, solvents used, production efficiency.

2.0.20 Exposure estimates related to production

Only applies to sites in the EEA. A brief description of the estimated exposure on the workplace, indirect to humans and to the environment, related to production. Numerical data are preferred.

Working environment

The most relevant moments of exposure should be described, for instance during filling, weighing, cleaning activities, sampling for quality and process control, in case of irregularities, etc. The estimated exposure in the workplace should be specified to the possible moments of exposure. if available, details concerning number of workers involved, level, route and duration of exposure should be provided for both during the working period and averaged over a longer period during working life.

Indirect exposure to humans

Environment

Information on process water consumption; (pre)treatment of waste water and/or flue gas; capacity and function of the waste water treatment plant; emission in kg/day to air; quantity of and concentration in produced chemical waste

2.0.30 Production sites (if available)

Give the information of the production location(s) only for those manufacturers sited in the EEA.

2.1.00 PROPOSED USES

2.1.10 Types of use; Use category

Indicate the general use category in coded or in non-coded form e.g. dyestuff, solvent, stabilizer (see the technical guidance for risk assessment or annexes 2 and 4 of this guidance for the use codes).

2.1.20 Desired effects

The main purpose(s) for which the substance is to be supplied should be given in coded form, e.g. colouring agent, solvent (see the technical guidance for risk assessment or annexes 3 and 4 of this guidance for the codes for desired effects).

2.1.30 Detailed information on envisaged uses:

Indicate in detail what effect is required e.g. imparting of brilliant fixed colour, medium for carrying active ingredients; U.V. light stabilizer in paints. Full content range should be given (e.g. 5-60%) for preparations(s) etc. and in final products.

Provide the following information (2.1.35) on paper, as it is not present in the SNIF proforma.

2.1.35 Statement, with relevant information, if the polymer has been developed to be environmentally degradable.

Give a statement, with relevant information, if the polymer has been developed to be environmentally degradable. Detailed information on test method and result should be given under section 5.2.00.

2.1.40 Form under which the substance is marketed

Give the information under which form the substance is placed on the market (for example as a preparation/product/substance as such).

If the substance is placed on the market as a preparation or product

- Trade name(s) of the preparation(s) and/or product(s)
- Form (e.g. granulate, paste, solution etc.)
- The maximum content and/or range in percentages of the substance in the preparation(s) and/or product(s).

2.1.50 Technological process(es) related to the use of the substance

A brief description of all technological process(es) related to the use of the substance or preparation including specification of the system in which the substance will be processed (open/closed, continuous/batchwise), duration and frequency of processing, maximum capacity per time-unit, pressure and temperature during processing, solvents used, processing efficiency.

Justify if the information is not available.

2.1.60 Exposure estimate(s) related to use

Give the information of the estimated exposure related to the use of the substance, in the workplace, to consumers, indirect to humans and to the environment. Numerical data are preferred.

Justify if the information is not available.

Workplace environment

The most relevant moments of exposure should be described, for instance during filling, weighing, cleaning activities, sampling for quality and process control, in case of irregularities, etc. The estimated exposure on the workplace should be given for all routes of exposure and be specified to the possible moments of exposure. If available, details concerning number of workers involved, level, route and duration and frequency of exposure should be provided for both during the working period and averaged over a longer period during working life. Also, the likely pattern of control should be provided.

Indirect exposure to humans

Environment

Information on process water consumption; (pre)treatment of waste water and/or flue gas; capacity and function of the waste water treatment plant; emission in kg/day to air; quantity of and concentration in produced chemical waste.

2.1.70 Fields of application with approximative breakdown

Give information on who (industry, Skilled Trades, or Public) will use the substance or preparation and in what proportions, e.g. industry, open systems, 60%; public at large, open systems, 40%.

Note: although a closed system is possible, under current guidelines the substance must be totally confined with no detectable release to the environment or exposure of workers under normal operating conditions, to justify such an entry. In practise some release might be expected during sampling, cleaning activities, weighing and in case of irregularities, during processing.

2.1.80 Identify of recipients

Give Name, Address, etc. of the recipient(s) of the substance or preparation. Do not complete if part of the legal entity of the notifier. Justify if the information is not available.

2.1.90 Waste quantities and composition of waste resulting from the proposed uses

Estimates or actual values of the waste quantities and composition of the waste resulting from the proposed uses should be provided where available. Justify if the information is not available.

2.2.00 ESTIMATED PRODUCTION IN AND/OR IMPORTS INTO THE EEA FOR EACH USE AND FOR EACH FIELD OF APPLICATION

2.2.01 Production and/or Imports

Indicate whether the substance will be produced in the EEA and/or imported from outside the EEA

2.2.01/02 Balance of the production and/or imports for the calendar year and the calendar years thereafter

Give the estimated production/imports in tonnes (a) for the remainder of the calendar year of notification and (b) for each calendar year thereafter (minimum of 3 years).

Note: if in the event the quantity is markedly different, the Competent Authority must be informed - as it should be for substances notified according to Annex VII A if the total tonnage supplied to the EEA exceeds 10, 100 or 1000 tonnes per calendar or cumulative totals of 50, 500, or 5000 tonnes year. A proposal for a material safety data sheet should be provided in the case that the notified substance should be classified and labelled. Ranges should be avoided if possible.

2.2.03 Estimated imports in case of sole representative.

Give the estimated production/imports in tonnes (a) for the remainder of the calendar year of notification and (b) for each calendar year thereafter (minimum of 3 years). In the case of more than 1 manufacturer the importers should be linked to his manufacturer.

2.2.10 Production and/or Imports Broken Down (in accordance with 2.1.10, 2.1.20, and 2.1.70)

For example:	During first year		
	1) as a solvent	Industry; open,	80%
		Public at large; open,	10%
	2) as a feedstock	Industry; open,	10%

2.3.00 RECOMMENDED METHODS AND PRECAUTIONS

For the recommended methods and precautions one has to consider the technological process, the exposure during use given by the types of use and the fields of application - as indicated under sections 2.1.10 and 2.1.20 - and all dangerous properties of the substance. In the case of several technological processes and several types of uses the recommended methods and precautions must be specified. The proposed precautions must be provided in concrete terms and should result in an effective protection of the exposed population and the environment. Only mentioning general recommendations, like prevent skin contact, does not satisfy. In addition, some substances which are not formally classified as dangerous following base-set testing (for example those with positive results in in-vitro short term tests for mutagenic or carcinogenic

properties, or where structure activity relationships (SAR) suggests potential to produce effects, such as respiratory sensitisation, not investigated at the base-set), may nevertheless still need to be treated as dangerous. For other not formally classified substances the provided information must specify methods and precautions to prevent excessive exposure. The information provided in this section should be consistent with the information in the material safety data sheet.

2.3.10 Handling

Engineering controls, in particular methods of controlling exposure at source, are preferable and should be described or referred to, e.g. available national codes of practice. These might be by total enclosure of the substance, partial enclosure and extraction equipment, or adequate general ventilation, as appropriate; also by the institution of safe systems of work/handling. Personal protective equipment should be advised only when other measures cannot adequately control exposure. Where personal protective equipment and clothing is advised, full specifications should be given (e.g. the type of dust mask required, referring to appropriate international standards; the design and composition of gloves etc.) Appropriate precautions should be given for substances which are flammable, oxidising, etc. (e.g. avoid sparks, naked flames; keep away from combustible material). Besides engineering controls and personal protective equipment, hygienic or organisational measures (e.g. administrative control) should be described.

2.3.20 Recommendations for proper storage

Considering the relevant dangerous properties, recommendations for safe storage should be given (e.g. ventilation system for the store rooms, type of container, conditions for storage, regulations for not storing the substance together with other substances, any necessary temperature regime).

2.3.30 Recommendations for transport

These should include the recommendations to enable safe movement of the substance within a factory to avoid hazards for workers. Of particular importance are the use of sufficiently resistant containers, movement in closed containers and measures to avoid the crushing of containers due to a fall during movement.

In addition, where international transport codes are known, these should also be specified, e.g. UN, IATA, EEC.

2.3.40 Fire hazards, (recommendation for appropriate extinguishing agents and nature of the products of combustion or pyrolysis)

Specify the nature of the combustion products (e.g. NO_X) are likely to arise during a fire (indicate if a test result) and indicate suitable extinguishing agents and personal protective equipment. If pyrolysis is likely during use or disposal, the reaction products, with their chemical compositions, should be given where these are known.

2.3.50 Other dangers, particularly reaction with water

In addition to dangers due to the substance, indicate whether it reacts with water to give, for example, toxic, explosive or flammable gases. Other dangers could be polymerisation reactions resulting in a large increase in volume, possibility of dust explosions, strongly exothermic reactions, possible respiratory sensitisation from a reactive dye, etc.

2.3.60 Dust explosion

Information on dust explosivity of the substance should be given. Test results should be given in section 3.1.40. If dust explosivity is likely precautions must be provided.

2.4.00 EMERGENCY MEASURES IN THE CASE OF ACCIDENTAL SPILLAGE

Give information on the appropriate measures for protection of man and the environment in the case of accidental spillage; e.g. "isolate the spillage", "evacuate personnel from the immediate vicinity", "absorb using inert material", "do not discharge to waste water system", etc.

2.5.00 EMERGENCY MEASURES IN THE CASE OF INJURY TO PERSONS

The information given here is intended for the purpose of immediate first-aid treatment. It is not intended to replace definitive diagnosis and treatment which can only be undertaken by a qualified doctor (specify to eyes, skin, ingestion and inhalation).

2.6.00 PACKAGING OF THE SUBSTANCE AND/OR PREPARATION

Give information how the substance/preparation should be packaged and transported; brief details of packaging for the various quantities and the type of container including material used for its construction (e.g. "polyethylene-lined 20 litre steel drums") should be given.

SECTION A3 PHYSICO-CHEMICAL PROPERTIES

Note: Where the relevant Annex V method provides for a number of possible alternatives, the specific procedure used should be identified in the "Methods" section.

3.0.00 NATURE OF THE SUBSTANCE

Give information on colour, physical state at 20°C and 101.3 kPa and the state (powder, crystalline, compact, viscous, etc.) of the substance.

Particle Size: where the substance is a powder, information on "aerodynamic" particle size distribution and the details of the test procedure should be given in section 3.1.50 and not in this section.

3.0.10 Melting Temperature/Freezing Temperature

Applies to solids and liquids with a melting point above 0°C Measurements should be taken up to 360°C or to decomposition if this occurs at a lower temperature. If decomposition occurs, the temperature of decomposition should be stated. For liquids the freezing temperature should be determined if above -20°C otherwise an indication from preliminary tests should be given. For viscous liquids, the 'Pour point' may be an acceptable alternative.

3.0.20 Boiling Temperature

Presumed to be measured at normal atmospheric pressure unless stated otherwise. Not applicable to gases or solids which either melt above 360°C or decompose before boiling (in which event give an estimate based on the result of section 3.4 or measure the boiling point under reduced pressure). If the substance does decompose before boiling, the temperature of decomposition should be stated.

3.0.30 Relative Density

Any variation from $D^{20}/14$ should be explained. Test report should include all weightings and calculations used to obtain the result.

3.0.40 Vapour Pressure

Vapour pressure is a key value for the estimation of exposure. Any volatile impurities should be first removed. A log p versus 1/T curve should be constructed with at least two values quoted in the 0-55°C range and an estimate given for 20 or 25°C. There is no need to measure if calculations indicate that the value is probably $< 10^{-5}$ Pa at 25°C. If a transition (change of state, decomposition) is observed, the following information should be noted: nature of the change, temperature at which the change occurs at atmospheric pressure, vapour pressure at 10 and 20°C above this temperature (unless the transition is from solid to gas). Although this parameter is more closely linked to section 3.0.20 than section 3.0.10, where a boiling point cannot be quoted due to decomposition and the melting point is above 360°C there is no need to attempt test

3.0.40; and for a melting point of < 360°C but > 200°C a limit value based on measurement or a recognised calculation method suffices.

3.0.50 Surface Tension (of aqueous solutions)

To be measured at or near 20°C using a solution of sufficient concentration such that any surface-activity potential is expressed; e.g. at 90% of saturation (quote concentration), to a maximum concentration of 1 g/l (where viscosity permits). If fairly soluble and surface-active, a measurement at a lower concentration should also be made. May be omitted where water solubility is very low, i.e. less than 1 mg/l.

3.0.60 Water Solubility

This should be determined at or near 20°C. If solubility/temperature dependence > 3% per °C then further measurements should be made at 10°C above and below the initially chosen temperature. The full test report should include calibration data required for the chosen analytical method and the readings for the test solutions. If the substance appears "insoluble" in water, the detection limit of the analytical method should be indicated.

3.0.70 Fat Solubility

The determination of fat solubility is not required any more at or below base set, but may be requested at higher levels of supply. The fat solubility should be measured at 37°C. Any reasonably stable liquid at 37°C triglyceride may be used. The fatty acid composition and other essential details of the fat/solvent used should be given in the full test report as should calibration data for the chosen analytical method and the readings for test solutions. If suspected on structural grounds or from initial tests that the substance will be "miscible in all portions", this should be checked by running tests at 37°C with substance concentrations of 5, 50 and 95%.

3.0.80 Partition Coefficient N-Octanol/Water

Even for those substances which are extremely soluble/insoluble in the two phases, an attempt should be made to provide a limit value (if necessary based on the individual solubilities in n-octanol and water). It is recognized that for surface-active substances, the measured result may only be approximate. The full test report should include calibration data required for the chosen analytical method(s) and the readings for test solutions. If the test cannot be performed, or it is impractical to do so, a calculated value for log P should be provided; details of the calculation method should be provided under "Method". Preferred methods are the Hansch and Leo method (see C. Hansch, A.J. Leo in Substituent Constants for Correlation Analysis in Chemistry and Biology, John Wiley, New York, 1979, and W. L. Lyman, W. F. Reehi, D. H. Rosenblatt (ed), Handbook of Chemical Property Estimation Methods, McGraw-Hill, New York, 1983) and the Rekker method (see R.F. Rekker, The hydrophobic gragmental constant, pharmacochemistry library, Elsevier, New York, 1977).

3.0.90 Flash Point

The closed cup method is the only acceptable procedure. This method is mainly applicable to liquids and (if knowledge of the flash point is necessary for safe handling), also to waxy or pasty substances and low melting point solids. If an open cup method has been used and the flash point is above 70°C it may be acceptable. In such circumstances, contact the Competent Authority.

3.1.00 FLAMMABILITY

This section covers a number of properties which are determined by a number of different test methods in Annex V; the relevant test methods should be given in the summary dossier. If any test is omitted (e.g. A12/A13) justification should be provided under "Comments" to the effect that experience indicates that either the result is expected to be negative, or that the substance will react violently under the conditions of the test.

3.1.10 Explosivity

These tests need not be carried out when available thermodynamic information (heat of formation, heat of decomposition) or absence of certain reactive groups in the structural formula (cf. Brethrick, Handbook of Reactive Chemical Hazards, Butterworths, London, 1979) or its "oxygen balance" (as indicated in the Institution of Chemical Engineers Booklet, 1957) establishes beyond reasonable doubt that the substance is incapable of decomposing, forming gases or releasing heat very rapidly.

3.1.20 Self Ignition Temperature (Auto-Flammability)

The test is not applicable to explosive compounds; and when carried out on a solid, the test (A16) is terminated at the melting point. Test A15 should be performed on waxy or pasty substances or very low melting point solids (<50°C) For substances with a low melting point (<l00°C) the advice of the Competent Authority should be sought. Test A15 should not be carried out when A16 gave a positive result. For test A15, the method used must be given under "Method".

3.1.30 Oxidizing Properties

This test is not applicable to liquids and gases, explosive or highly flammable substances, organic peroxides or to combustible solid substances liable to melt under the conditions of the test. In addition, the test is not applicable if it can be demonstrated, for example on the basis of the chemical structure, that the substance is incapable of reacting exothermically with combustible materials. With cellulose as the combustible substance, false positives may occur if the test substance shows increased flammability rather than oxidizing properties. The test should be repeated using an inert substance, such as kieselguhr, and/or with cellulose in an inert atmosphere. Detailed guidance is available from the Competent Authority.

3.1.40 Additional Physico-Chemical Properties

Details of additional tests, e.g. viscosity, stability tests, dust explosion tests etc. should be included here.

3.1.50 Particle Size

In case the substance is a powder, a particle distribution measurement should be provided. A full test is not required if no particles less than 100 microns are present.

3.1.60 More Physico-Chemical Tests

General:

Additional tests especially required for polymers.

Test

1. Molecular weight distribution
2. Thermal weight distribution
3. Extractivity

Water solubility of polymers. See item 3.0.60.

SECTION A4 TOXICOLOGICAL STUDIES

4.1.00 ACUTE TOXICITY

General

Substances other than gases should be tested by oral administration (4.1.10) and either by the dermal or inhalation route dependent upon the nature of the substance and the likely route of human exposure. In the case of fine powders. (see 3.1.50: there is as yet no agreed rule linking that result to a presumptive use of the inhalation route, but one current suggestion is that the presence of >10 % of particles <10 microns MMAD should be considered strongly indicative), consideration should be given to testing by the inhalation route. Gases should be tested by the inhalation route alone. Volatile liquids should be tested by the oral and inhalation routes. The notifier should include a justification for the choice of the second exposure route in the 'Comments' section. The technical guidance documents related to the risk assessment Directive 93/67/EEC provide criteria for the selection of the relevant exposure route.

4.1.10 Administered orally

4.1.11 Complete LD_{50} toxicity procedure

Classification	Indicate how/if classified as a result of this test; enter 'T+' (very toxic), 'T' (toxic), 'Xn' (harmful), or NC' (Not Classified) only.
Limit test	Single character entry. Indicate **Y**(es) or **N**(o)
LD_{50}	One value should be given. If both sexes are tested at each dose level, then the combined LD_{50} should be stated. Where there is a significant difference in response between the sexes (i.e. greater than two-fold) this should be reported in the "Comments" section. If the LD_{50} is determined on only one sex with a confirmatory study on the other sex at only one dose level, the LD_{50} value is stated here and information on the result of the confirmatory study is given in the "Comments" section.
95% Confidence	Give the confidence limits of the reported LD_{50} limits
Slope of dose	Express the slope in probit units per $\log_{10}$ dose mortality curve
Species/strain	Specify the species/strain of the test animal, e.g. Wistar (SPF) rat, Sprague Dawley rat. The rat is the preferred species.
Vehicle	Give its composition before test substance is added e.g. 2% aqueous-carboxymethyl cellulose, propylene glycol. Indicate whether the test substance is in solution or suspension.
Results	Deaths to be given in the form of a table showing sex/dose given/no of animals/no of deaths should be those considered to be due to the test substance. Information on any other deaths should be given briefly under "Comments".

Sex Dose (mg/kg)
Number of animals
Number of deaths

This is a Table, structured for entry of one text character (Sex), and three numeric entries. Unit (mg/kg) for the numeric entry for the dose is pre-defined in SNIF, therefore enter only numeric values in these fields.
A typical entry might be as follows:

M	2000	5	0
F	2000	5	0

Signs of toxicity

The signs listed should only be those considered to be due to the test substance. They should be related to dose level, time of onset and duration. It may be appropriate to indicate the time of deaths, especially if they are delayed. If animals appear to recover completely, appropriate details should be given. If it is considered there were no substance-related signs of toxicity, this is stated.

Effects in organs

The effects listed should only be those considered to be due to the test substance and indicate their relationship to dose level. If a difference in effects is observed between animals that died/were killed in extremis during the study and those killed at termination, then note separately. If it is considered that there were no substance related effects on organs, this should be stated.

Method

e.g. 87/302/EEC, B1 (Acute oral toxicity)

Body responsible for test

Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.

Comments

It is sometimes pertinent to state whether the highest concentration tested was the maximum attainable.

4.1.12 Fixed-dose toxicity procedure

Classification

indicate how/if classified as a result of this test; enter 'T+' (very toxic), 'T' (toxic), 'Xn' (harmful), or 'NC' (Not Classified) only.

Discriminating dose

Which of the 4 fixed doses is indicated (5, 50, 500 or 2000 mg/kg bw).

Preliminary sighting study

Number of animals

Give the number of males and female in the preliminary sighting study.

Species/strain

Specify the species/strain of the test animal, e.g. Wistar (SPF) rat, Sprague Dawley rat. The rat is the preferred species.

Results

Evidence of toxicity and mortality should be summarised in a table showing the fixed doses administered; enter 'Y' (Yes) or 'N' (No) only. Additional doses not shown already in the table should be added.

Observations

Enter any effects observed in the preliminary study.

Main study

Number of animals

Give the number of males and female in the main study

Species/strain	Specify the species/strain of the test animal. The rat is the preferred species.
Vehicle	Give its composition before test substance is added e.g. 2% aqueous-carboxymethyl cellulose, or write 'None'. Indicate whether the test substance is in solution or suspension.
Results of the initial(I) and further(F) dosing	Evidence of toxicity and mortality should be summarised in a table showing sex/the fixed doses specified in the 92/69/EEC test method (i.e. 5, 50, 500 and 2000 mg/kg)/number of animals/number of deaths. Dose levels other than those specified are not acceptable in the main study.
Observations	Include any notable observations that cannot be entered in the section below.
Signs of toxicity	The signs listed should only be those considered to be due to the test substance. They should be related to dose level, time of onset and duration. It may be appropriate to indicate the time of deaths, especially if they are delayed. If animals appear to recover completely, appropriate details should be given. If it is considered there were no substance-related signs of toxicity, this is stated.
Effects in organs	The effects listed should only be those considered to be due to the test substance and indicate their relationship to dose level. If it is considered that there were no substance related effects on organs, this should be stated.
Method	e.g. 92/69/EEC, Bl.bis (Acute oral toxicity - Fixed Dose Procedure)
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	It is sometimes pertinent to state whether the highest concentration tested was the maximum attainable.

4.1.20 Administered by Inhalation

Classification	Indicate how/if classified as a result of this test; enter 'T+' (very toxic), 'T' (toxic), 'Xn' (harmful), or 'NC' (Not Classified) only.
Limit test	Single character entry. Indicate **Y**(es) or **N**(o)
LD_{50}	One value should be given. If both sexes are tested at each dose level, then the combined LD_{50} should be stated. Where there is a significant difference in response between the sexes (i.e. greater than two-fold) this should be reported in the "Comments" section. If the LD_{50} Is determined on only one sex with a confirmatory study on the other sex at only one dose level, the LD_{50} value is stated here and information on the result of the confirmatory study is given in the "Comments" section.
95% Confidence limits	Give the confidence limits of the reported LD

Slope of dose mortality curve	Express the slope in probit units per $\log_{10}$ dose
Species/strain	Specify the species/strain of the test animal, e.g. Wistar (SPF) rat, Sprague Dawley rat. The rat is the preferred species.
Exposure period (hours)	Enter the daily exposure period as an integer
Method of exposure	This would be 'whole body', 'oro-nasal', or 'head only'.
Physical form	Enter 'S' (solid), 'L' (liquid), or 'G' (gas) only.
Mass median aero-dynamic diameter (for liquid and solid aerosols)	The MMAD of particles to which animals were exposed is stated. In addition, some indication of the range of particle sizes should be given, e.g. 2.2μ, or 75% of particles < 5μ.
Vehicle	Give its composition before test substance is added e.g. 2% aqueous-carboxymethyl cellulose, propylene glycol. Indicate whether the test substance is in solution or suspension.
Results	Deaths to be given in the form of a table showing sex/dose given/no of animals/no of deaths should be those considered to be due to the test substance. Information on any other deaths should be given briefly under "Comments".
Sex Conc (mg/l) Number of animals Number of deaths	This is a Table, structured for entry of one text character (Sex), and three numeric entries. Unit (mg/l) for the numeric entry for the concentration is pre-defined in SNIF, therefore enter only numeric values in these fields. A typical entry might be as follows: M 5.10 5 0 F 5.10 5 0
Signs of toxicity	The signs listed should only be those considered to be due to the test substance. They should be related to dose level, time of onset and duration. It may be appropriate to indicate the time of deaths, especially if they are delayed. If animals appear to recover completely, appropriate details should be given. If it is considered there were no substance-related signs of toxicity, this is stated.
Effects in organs	The effects listed should only be those considered to be due to the test substance and indicate their relationship to dose level. If a difference in effects is observed between animals that died/were killed in extremis during the study and those killed at termination, then note separately. If it is considered that there were no substance related effects on organs, this should be stated.
Method	e.g. 87/302/EEC, B2 (Acute inhalation toxicity)
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.

Comments It is sometimes pertinent to state whether the highest concentration tested was the maximum attainable.

4.1.30 Administered Cutaneously

Classification Indicate how/if classified as a result of this test; enter 'T+' (very toxic), 'T' (toxic), 'Xn' (harmful), or 'NC' (Not Classified) only.

Limit test Single character entry. Indicate **Y**(es) or **N**(o)

LD_{50} One value should be given. If both sexes are tested at each dose level, then the combined LD_{50} should be stated. Where there is a significant difference in response between the sexes (i.e. greater than two-fold) this should be reported in the "Comments" section. If the LD_{50} Is determined on only one sex with a confirmatory study on the other sex at only one dose level, the LD_{50} value is stated here and information on the result of the confirmatory study is given in the "Comments" section.

95% Confidence limits Give the confidence limits of the reported LD_{50}

Slope of dose mortality curve Express the slope in probit units per $\log_{10}$ dose

Species/strain Specify the species/strain of the test animal, e.g. Wistar (SPF) rat, Sprague Dawley rat. The rat is the preferred species.

Exposure period (hours) Enter the daily exposure period as an integer, e.g. 24 (hours)

Type of dressing Enter 'O' (Occlusive) or 'S' (Semi-occlusive)

Vehicle Solids should only be moistened with e.g. water or corn oil. Liquids are generally tested undiluted.

Results Deaths to be given in the form of a table showing sex/dose given/no of animals/no of deaths should be those considered to be due to the test substance. Information on any other deaths should be given briefly under "Comments".

Sex Dose (mg/kg) Number of animals Number of deaths This is a Table, structured for entry of one text character (Sex), and three numeric entries. Unit (mg/kg) for the numeric entry for the dose is pre-defined in SNIF, therefore enter only numeric values in these fields. A typical entry might be as follows

M	2000	5	0
F	2000	5	0

Signs of toxicity The signs listed should only be those considered to be due to the test substance. They should be related to dose level, time of onset and duration. It may be appropriate to indicate the time of deaths, especially if they are delayed. If animals appear to recover completely, appropriate details should be given. If it is considered there were no substance-

	related signs of toxicity, this is stated. Effects at the site of application (local) and systemic effects are distinguished.
Method	e.g. 92/69/EEC, B3 (Acute inhalation dermal)
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	it is sometimes pertinent to state whether the highest concentration tested was the maximum attainable.

4.1.50 Skin Irritation

General

This test should not be conducted with strongly acidic or alkaline substances (see current OECD test guidelines). The testing of substances which have been shown to be very toxic by the dermal route may be unnecessary.

In some studies the test substance will have been applied to both intact and abraded skin; the latter procedure is additional to Annex V guidelines and is not used for classification and labelling purposes. If it is considered necessary to report results for abraded skin it is essential that this cannot lead to confusion, and results from abraded skin should be described in the section "Other observations" and clearly indicated as relating to abraded skin.

Classification	Indicate how/if classified as a result of this test; enter 'C' (Corrosive), 'Xi' (Irritant), or 'NC' (Not Classified) only.
Species/strain	Specify the species/strain of the test animal. The rabbit is the preferred species, e.g. rabbit NZW (New Zealand White).
Number of animals	Give the number of animals tested.
Duration of exposure	Give the duration of exposure in hours.
Amount of substance	Give the amount in mg.
Type of dressing	Enter 'O' (Occlusive) or 'S' (Semi-occlusive) only.
Vehicle	Give its nature and composition, e.g. moistened with water
Reversibility of any observes effects	In interpreting the results it is essential to have information on the reversibility of the observed effects. Therefore, notifiers are required to indicate whether the effects were fully reversible and, if so, within what time period. If the effects were not fully reversible, the length of the observation period must be stated (if less than 14 days, justification must be provided under "Comments"). In addition, maximum scores at the end of the observation period should be stated in the table of "Overall results" (see below).

Overall results The overall results should be given in the form of a table. The scores refer to intact skin only.

If 3 animals or less were used, mean scores for each animal are given for each end-point (erythema/eschar and oedema). If more than 3 animals were used, one overall mean score is given for each end-point.

The mean scores are calculated as indicated in Commission Directive 93/21/EEC. The "maximum value" is defined as the maximum individual score for any animal during the whole observation period (not limited to the 24-72 hour period). The "maximum duration of any effect" is defined as the longest period in days during which an irritant response (of any severity) was seen in an animal. The "maximum value at the end of the observation period" is the maximum score for each end-point in any animal at the end of the observation period. This information is only required if the effects were not fully reversible (see "Reversibility of any observed effects").

Other observations Erythema/eschar and oedema: sufficient details will often have been provided under "Overall results" but in some cases it may be appropriate to describe reactions seen before the 24 hour reading (or after the 72 hour reading). Details of other effects, especially of a serious nature, seen during the study should be given e.g. type of effect, severity, number of animals affected and duration. Where the test substance produces discolouration of the skin such that interpretation of the effects is made difficult, additional information e.g. histopathological or skin fold thickness should be given. If a study is terminated before the 72 hour reading because of severe skin irritation or corrosion, the "Overall results" entry cannot be completed and therefore full details must appear under this section including motivation for the scores and the proposed classification and labelling.

Method e.g. 92/69/EEC, B4 (Acute toxicity - Skin irritation)

Body responsible for test Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.

Comments Comments should be made on any aspects of the test which may influence the results. Comments should be full but concise

4.1.60 Eye Irritation

General

Strongly acidic or alkaline substances and substances which have demonstrated define corrosivity or severe irritant properties in a dermal irritation study, or in other studies, should not be tested for eye irritation (see current OECD test guidelines).

In some studies the effect of irrigating the eye following application of the test substance will have been investigated. However, normally only results from non-irrigated eyes are used for classification. If results from irrigated eyes are reported, they should be given under the section "Other observations" and should be clearly indicated as relating to irrigated eyes.

Classification	Indicate how/if classified as a result of this test; enter 'C' (Corrosive), 'Xi' (Irritant), or 'NC' (Not Classified) only.
Species/strain	Specify the species/strain of the test animal. The rabbit is the preferred species, e.g. rabbit NZW (New Zealand White).
Number of animals	Give the number of animals tested.
Nature of the substance	The entry here would be for example: powder or undiluted liquid
Amount of the substance	The entry here would be for example: 0.1 g for powder or 0.1 ml for liquids or diluted solids.
Reversibility of any observed effects	See entry under section 4.1.50; however, for this test, justification must be provided under "Comments" if the observation period was less than 21 days.
Overall-results	See entry under section 4.1.50. The values quoted apply to unirrigated eyes.
Other observations	Ocular lesions will have been described under "Overall results" but in some cases it may be appropriate to describe reactions seen before the 24 hour reading (or after the 72 hour reading). Details of other effects, especially of a serious nature, seen during the study should be given e.g. type of effect (e.g. lacrimation, discharge), severity, number of animals affected and duration. If a study is terminated before the 72 hour reading because of severe eye irritation, the "Overall results" entry cannot be completed and therefore full details must appear under "Other observations" including motivation for the scores and the proposed classification and labelling.
Method	e.g. 92/69/EEC, B5 (Acute toxicity - Eye irritation)
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	If the observed effects were such as to require the use of Risk Phrase R41, this should be stated.

4.1.70 Skin Sensitisation

General

A test in the guinea-pig is required: if the substance can be applied intradermally, the Maximisation test is the highly preferred method. If it is not technically possible to conduct the Maximisation test and the Buehier test is used, the reason should be given. The intradermal and dermal induction concentration is adjusted to the level that produces evidence of skin irritation (score 112), but that is well tolerated by the animals in each induction stage. Where the test substance does not induce irritation, the test should be carried out with the highest concentration and with due provision for optimal skin penetration (pretreatment with 10% sodium lauryisulfate solution). The maximum induction concentration of 25% for solids used at first by Magnusson and Kligman cannot be considered as an absolute limit value (see also Kligman & Basketter,

1995, in Contact Dermatitis 32); liquids if appropriate should be applied directly. The choice of the vehicle should be justified.

Classification	Indicate how/if classified as a result of this test; enter 'Xi' (Irritant), or 'NC' (Not Classified) only.
Species/strain	Specify the species/strain of the test animal. The guinea-pig is the required species, e.g. female albino Dunkin-Harley guinea pig
Number of animals in test group	Give the number of animals tested.
Number of animals in negative control group	Give the number of animals in the control group.
Maximum conc. not giving rise to irritant effects in preliminary test	This should be addressed.
Conc. of test material used at induction	Give the intradermal and the dermal concentration of the test substance in each induction
Conc. of test material used at challenge	Give the dermal concentration of the test substance in the challenge stage.
Signs of irritation during induction	This is important information as it can indicate whether a satisfactory dose level was used for induction.
Results	In the main body of the table given for summarising the test results, the term "skin reaction" includes both irritation and/or sensitisation effects. Beneath the main table in the sub-section headed %umber of animals showing evidence of sensitization at each challenge concentration", the number of animals showing a true sensitization response should be stated. Ideally there should be no skin reactions in the negative control animals at challenge. In such a case the incidence of sensitisation is equivalent to the incidence of skin reaction in the test group. Interpretation can become difficult when skin reactions are seen in negative control animals. Data for all challenge concentrations and times should be provided. If a second challenge is performed the time interval between the first and second challenge should be stated under "Other observations".
Method	The type of test e.g. Buehier, Maximisation should be stated, e.g. 92/89/EEG, B6 (Guinea Pig Maximization Test). Details should be provided if the method used differs from the standard method for a particular test, e.g. the use of only dermal application of the test substance in a Maximisation test.
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.

Comments A statement justifying the dose levels used for both induction and challenge should be made. It may be appropriate to comment on the basis for deciding whether skin reactions at challenge were evidence of sensitisation or irritation (e.g. comment on magnitude of skin responses seen). Any problems of interpreting test results arising from discoloration of the skin by the test substance should be identified. Where histological studies are used to differentiate between irritant and sensitising effects these should be described.

4.2.00 SUBACUTE TOXICITY

General

Oral, inhalation and dermal route of application should be considered. The decision for a certain route depends on the proposed uses of the substance, the results of its acute toxicity tests and on its physico-chemical properties. The dermal route should be avoided if the substance obviously does not penetrate the skin, as indicated by water and fat solubility and by the results of the dermal acute toxicity test. Generally the preferred route is the oral one (see also the "General" comments at start of section 4.1.00). The choice of the route of administration must be justified.

A report of a sub-acute toxicity study requires particularly careful and critical assessment. Only effects that are considered to be due to the test substance should appear in the summary document. The usefulness of a summary is increased greatly if responses are quantified (e.g. number of animals affected, magnitude/severity of effects, time of onset and duration) and any dose/concentration response is mentioned. Important effects should be described quantitatively as a deviation from the values seen in the control animals. Emphasis should be given to effects of toxicological significance, but it should also be indicated if effects were observed which were considered not to be of toxicological significance. Statistically significant differences occurring merely by chance should not be reported. If animals appear to recover completely, details should be provided, and results of any recovery-group experiment should be reported. If no signs of toxicity considered to be due to the test substance were seen this should be stated.

4.2.10 Sub-Acute Toxicity 28/90 day-test

The strategy for assessing the requirement for further repeated-dose studies at higher supply levels is described in the Technical Guidance.

See for section 4.1.11 and in addition:

Classification Indicate how/if classified as a result of this test; enter 'T' (Toxic), 'Xn' (Harmful), or 'NC' (Not Classified) only.

Limit test (Y/N) Single character entry. Indicate **Y**(es) or **N**(o).

Route of administration e.g. Oral, Dermal, or Inhalation, etc. In SNIF, only two characters are available for this entry, as follows:

OR (oral)	DM (dermal)	IN (inhalation)
IV (intra-venous)	M (intra-muscular)	JP (intra-peritoneal)
SU (sub-cutaneous)		

Dose or conc. at which no toxic effects were observed

This is the doses or concentration at which no substance-related toxicologically significant adverse effects were observed. It should be noted that this dose level indicating the level at which "serious damage to health" is observed (i.e. the dose level at which R48 is applied) will usually be higher than at which "no effects" were observed.

Mg/kg/day or, m/1/…/h/day

Enter value.
If not established, give '<' lowest dose used in the study.

Species/strain

Specify the species and (strain) of the test animal, e.g. Rat Wistar). The Rat is the preferred species. However data from studies using other species can be useful and should not be rejected.

Method of administration

Eg. gavage, diet, occlusive/semi-occlusive dressing, nose-only, etc.

Vehicle

The vehicle should be described clearly and in full (not abbreviated). Also, state whether the test substance is in solution or suspension. SNIF permits up to 60 characters for this entry.

Mass median aero-dynamic diameter (for liquid and solid aerosols)

The MMAD of particles to which animals were exposed is stated. In addition, some indication of the range of particle sizes should be given, e.g. 2.2μ, or 75% of particles < 5μ.

Duration of exposure per day

Give the duration exposure in hours per day by inhalation or dermal.
Enter the daily exposure period as an integer

Dosing regime

5 or 7 days/week. Enter '5' or '7' only.

Number of animals doses, group number

The purpose of this summary table is to allow referral to group numbers in the results section and hence facilitate presentation. Any recovery group should be identified and given group numbers different to the main test groups. Dose or concentration must be in mg/kg or mg/l. A typical entry might be the following:

	Sex	**No. of Animals**	**Dose or concentration**
1	M	5	0
2	M	5	500
3	M	5	1000
1	F	5	0
2	F	5	500
3	F	5	1000

Results

Where appropriate, signs listed should be related to exposure level, time of onset and duration. If animals appear to recover completely, details should be provided and results of any recovery-group experiment should be reported. If no signs of toxicity were seen and considered to be due to

	the test substance, this should be stated. Important effects should be described quantitatively, as a deviation from the values seen in the control animals.
1. Clinical observations	Free Text. Clear, concise and organised. Signs listed should only be those considered to be due to the test substance. Clinical observations include deaths, effects on body weight, food and water consumption, and any signs of ill-health, e.g. no deaths occurred and no sign of toxic effect observed; body weight gain slightly reduced in Groups 3, 4 and 6 during the period of dosing, but returned to control values by end of the recovery period in Group 6.
2. Laboratory findings	As 1) above, covering haematology, blood chemistry and urinalysis values e.g. No significant treatment-related changes to indicate a toxic effect.
3. Effects in organs	Summarise observations at necropsy (macroscopic) and at microscopic examination. It may be appropriate to distinguish effects seen in animals that died during the study from those in animals killed at termination. Results of interim or recovery animals should be reported. The effects listed should only be those considered to be due to the test substance, e.g. macroscopic effects, weight changes, microscopic effects, and are related to exposure level. Effects should be described quantitatively as a deviation from the control animals.
Dose or conc. at which no effects	This is the dose or concentration at which no substance-related toxicologically significant effects were observed. It should be noted that were observed this dose level would usually be lower than that at which "No toxic effect" (Serious damage to health) is observed. If not established, give '<' lowest dose in this study.
Method	e.g. OECD 407
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	Include here any information to explain the absence of entries to key fields above, or to clarify the interpretation of the study. If dosing was conducted in diet, or in drinking water, include calculated values, in mg/kg, for mean daily dosing. Comment on the no toxic effect level, or on observed principal effects: e.g. It is not possible to establish a reliable and unequivocal no toxic effect level for this substance. e.g. As the effects observed at 100 and 1000 mg/kg were only minor, the dose at which no toxic effect occurred is considered to be 1000 mg/kg. e.g. The primary target organ was the liver. The weights and pathology of the other organs did not differ significantly from controls.

Note if a study is unacceptable, and why:

e.g. The 90 day inhalation study was unacceptable because of severe and persistent intercurrent respiratory disease in all groups, including controls.

Justification for the classification and labelling proposed (on the basis of the results of this test) may be necessary.

4.3.00 MUTAGENICITY

General

At the base-set (Annex VII A) two mutagenicity tests are necessary, and at the reduced set (Annex VII B/C) only one mutagenicity test is necessary: one bacteriological for gene mutation (required at the reduced set) and one non-bacteriological for chromosomal aberrations. In order to maximise the detectability of any potential mutagenic hazard, and for the reason of animal welfare, the nonbacteriological test should be an in-vitro test.

If after full and careful evaluation of the results of the test, it is not possible to conclude whether an overall result is definitely positive or definitely negative, that result has to be considered equivocal. In such a case, the equivocal response is recorded under "Observations" and "Comments" but neither "Result" box is ticked.

In the event of a positive result in either test, further testing according to the strategy as described in the technical guidance documents for risk assessment for new substances should be carried out.

For level 1 and level 2 the strategy for assessing the requirement for collecting further information to elucidate the mutagenic potential of a notified substance at higher supply levels is described in the Technical Guidance.

The testing requirements at higher levels of supply are determined by considering at any stage in the life progress of a substance all information known to that point in relation to its mutagenic potential and intended use.

4.3.10 Bacteriological Test

These notes apply to Annex V, tests B. 13 and B. 14.

Type of bacterial strain	Salmonella typhimurium (e.g. TA1535, TA1537, TA1538, TA98, TA100) Escherichia coli.
Conc. range in the main test	Give the range of concentrations used in the main test with and without metabolical activation.
Conc. producing toxicity	Indicate which minimal concentration in the preliminary and in the main test both with and without metabolical activation shows toxic effects to bacteria.
Solvent	Give the identity of the solvent.
Conc. resulting in precipitation	Concentration in microgram per plate.

Metabolic activation system Enter the details of the metabolic activation used, e.g. Aroclor-induced rat liver S9, or Phenobarbital/β-naphthoflavone-induced rat liver S9.

Observations For equivocal or positive results some details of the response observed for named strains should be given, e.g. magnitude of the increase in revertants, plus any dose response. It should be stated whether results were confirmed in an independent experiment.

Result It should be stated whether the overall result is considered to be negative or positive for both (a) experiments with metabolic activation and (b) experiments without metabolic activation.

Method If, in order to make for a more informative test, the protocol differs from the Annex V bacteriological test, appropriate details should be provided, e.g. use of pre-incubation, use of a positive control that is structurally related to the test substance.

Body responsible for test Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.

Comments If an overall negative result has been obtained (either with or without activation) it is necessary to comment on the adequacy of the test, e.g. provide justification for the dose levels used and for the type of metabolising system in relation to the structure of the test compound, and to state whether positive controls gave a satisfactory response.

4.3.20 Non-Bacteriological in vitro,

General

These notes apply to test B.10 which is designed to detect primarily structural chromosome aberrations. If effects on chromosome number (ploidy effects) have been investigated as well, additional information is required under "Observations" and "Result".

Type of test Data collection for the tests listed below is achieved by using the same/similar proforma for all tests. Thus data-fields exist in the proforma to collect relevant information, but for any individual test some fields may be redundant.

4.3.21 IN VITRO MAMMALIAN CYTOGENWY (B10)
4.3.22 IN VITRO MAMMALIAN CELL GENE MUTATION (B17)
4.3.23 UNSCHEDULED DNA SYNTHESIS - MAMMALIAN CELLS IN VITRO (B18)
4.3.24 SISTER CHROMATID EXCHANGE ASSAY IN VITRO (B19)
4.3.25 IN VITRO MAMMALIAN CELL TRANSFORMATION (B21)
4.3.26 GENE MUTATION - SACCHAROMYCES CEREVISIAE (B15)
4.3.27 MITOTIC RECOMBINATION - SACCHAROMYCES CEREVISIAE (B16)

Type of cell used Describe, e.g. Chinese hamster V79 lung cells; mouse lymphoma L5178Y cells; rat hepatocytes; human lymphocytes; etc.

Conc. range in the main test (μg/ml)	Units (μg/ml) are assumed in SNIF, so enter only the numeric values. Enter the range of concentrations used in the main test, with and without metabolic activation. Only a single line entry is allowed. Give the range tested in the first experiment, and provide details of the second experiment in the 'Comments' section.
Conc. producing toxicity	Indicate which minimal concentration in both preliminary and main tests with and without metabolical activation shows toxic effects to bacteria. A s inferred from e.g. the mitotic index; the degree of toxicity in both preliminary and main tests should be stated.
with metabolic activation	e.g. 5-1000
without metabolic activation	e.g. 5-1000
Conc. producing toxicity	Indicate which minimal concentration in both preliminary and main tests, with and without metabolic activation, shows toxic effects to the test system.
a) In a preliminary test	
with metabolic activation	e.g. >1000
without metabolic activation	e.g. >1000
b) In the main test	
with metabolic activation	e.g. >1000
without metabolic activation	e.g. >50
Vehicle	The vehicle should be described clearly and in full (not abbreviated). Also, state whether the test substance is in solution or suspension. SNIF permits up to 60 characters for this entry. e.g. dimethyisuifoxide, arachis oil BP, distilled water.
Exposure period	This is the period of time, in hours, the cells are exposed to (incubated with) the test substance and should be completed for all test methods. The time-unit (hours) is pre-defined in SNIF. Enter numerical value only. Only a single numeric entry is permitted. Therefore, if more than one value is available, e.g. 20 and 44 hours, enter only the first value, and then enter all values in text in the 'Comments' section.
with metabolic activation	e.g. 3
without metabolic activation	e.g. 20

Expression time Free Text, or leave blank if not applicable. This applies to 4.3.22 and 4.3.26. It relates to the period of time the cells are maintained in growth medium to allow induced mutations to be detected. Example values are, for the mouse lymphoma test, 3 days, and for the CHO mammalian cell gene mutation assay, 7 days.

Selection time Free Text, or leave blank if not applicable. This applies to 4.3.22 and 4.3.26. It relates to the period of time the cells are incubated with a selection agent, such as 6-thioguanine or trifluorothymidine, in order to determine the mutation frequency.

Fixation time Free Text, or leave blank if not applicable. This equates to the harvest time. It is the period between the start of exposure to the test substance and the fixation or harvest of the cells. Values are required for 4.3.21, 4.3.23 and 4.3.24.

Metabolic activation system Enter the details of the metabolic activation used, e.g. Aroclor-induced rat liver S9, or Phenobarbital/β-naphthoflavone-induced rat liver S9.

Observations In the case of tests with negative results, comment on the acceptability of control data. Also, comment on any precipitation observed. For equivocal or positive results, provide details of any response observed, e.g. type of structural damage, magnitude of effect, and any dose response. Similar information is required if ploidy effects have been investigated. In 4.3.23, indicate if large and small colonies were scored. Some example entries are given below:

e.g. Reproducible increases (5.5-8.5% above the concurrent control values of 0-1 %) in the number of chromosomal aberrations (excluding gaps) occurred at 4000-5000 μg/mi (+S9).

e.g. No significant or dose-related increases in the frequency of cells with aberrations were seen in either the first or second experiment.

e.g. The positive control, cyclophosphamide, induced a significant and large increase in the frequency of aberrations. Negative control values were within the normal range.

e.g. Responses obtained from the negative and positive controls demonstrated that the system was capable of detecting chemicals that caused chromosomal damage.

Results Only a single character entry ('+', '-', or '0') is permitted:(if equivocal '0', tick 'see comments' box). In cases where '0' is entered (equivocal), further explanation should be provided in the 'Comments' section. If ploidy effects have also been investigated, the overall result for this end-point should also be stated in the 'Observations' section.

with metabolic activation (+/-) +

without metabolic activation (+/-) -

Method (type of test)

Clearly indicate the source of the test-method protocol, e.g. 87/302/EEC or 92/69/EEC, OECD, or quoted publication, and the type of test, e.g. (metaphase analysis), or (UDS-autoradiography). It is preferred that approved test methods are used, if possible. However, other methods may be used when necessary provided they are well validated and/or scientifically justified. The choice of test-method should have been made by discussion with the Competent Authority, and scientific justification included in the test report.If a separate confirmatory study has been performed this should be reported in a separate entry (use function 'Add' in the SNIF proformat).

Body responsible for test

Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.

Comments

Free Text. Include any additional information. If an overall negative result has been obtained (either with or without metabolic activation) or if there are data on the effect of the chemical on cell cycle time, it is necessary to comment on the adequacy of the test.

Comment on any problems that make the result neither a clear positive nor a clear negative.

In 4.3.25, 4.3.26 or 4.3.27, a brief description of the procedure should be included.

Describe additional experiments not covered by previous entries (e.g. repeat experiments with additional exposure or fixation times).

Give method and criteria for assessment of toxicity. This may include a significant reduction (50 %) in mitotic index, degree of confluency or cell counts, or a low relative cloning efficiency (<10 %).

Justify any (apparently) unusual conditions as well as deviations from approved test

In 4.3.21, two typical entries are as follows:

a) Toxicity was observed as a decrease in mitotic index >50%. An additional fixation time of 48 hours was employed with S9. The concentration range in this test was 10-1000 μg/ml, and toxicity was observed at 700 μg/ml and above.

b) The duration of the cell cycle of the CHO strain used is 12-13 hours. The treatment and recovery periods therefore correspond to 1.5 times a cell cycle (18 hours) and to 1.5 times a cell cycle plus 24 hours (42 hours).

4.3.30 Non-Bacteriological Test in vivo

General

These notes apply to Annex V tests B.11 (cytogenetics) and B.12 (micronucleus). The cytogenetics assay is designed to detect primarily structural chromosome aberrations. If effects

on chromosome number (ploidy effects) have been investigated as well, additional information is required under "Observations" and "Result".

Type of test

Data collection for the five tests listed below is achieved by using the same/similar proforma. Thus data-fields exist in the proforma to collect relevant information, but for any individual test some fields may be redundant. For other in vivo tests, individual proformas are provided and are illustrated later.

4.3.31 IN VIVO MAMMALIAN BONE MARROW CYTOGENETICS (B1l)
4.3.32 IN VIVO MAMMALIAN BONE. MARROW MICRONUCLEUS (B12)
4.3.33 IN VIVO MAMMALIAN GERM-CELL CYTOGENETICS (B23)
4.3.38 UNSCHEDULED DNA SYNTHESIS (IN VIVO/IN VITRO)

4.3.39 In vivo mammalian bone marrow sister chromatid exchange (SCE)

Species/strain
Sex Dose (mg/kg)
Number of animals
Sacrifice times

Specify the species/strain of the test animal.
This is a Table, structured for entry of one text character (Sex), and three numeric entries. Units (mg/kg and hours) for two of the numeric entries are pre-defined in SNIF, therefore enter only numeric values in these fields.

In 'Sacrifice times', there is a 'from - to' range.

In 4.3.31 or 4.3.32, a typical entry might be as follows

M	2000	5	24	48
F	2000	5	24	48

Doses producing toxicity

For a cytogenetics assay, details of the effects on mitotic index should be given. For a micronucleus assay, details of the effect on the polychromatic/normochromatic erythrocyte ratio should be given. In addition, for either assay, any evidence for a maximum tolerated dose (e.g. death clinical signs of toxicity) should be stated. If no toxic effects were observed this should be stated. In fact, SNIF does not provide headings, but this information can be entered as required.

i.e. Mitotic Index: e.g. >= 1000 μg/ml
PIN Ratio: e.g. No effect seen

Other toxic signs:
- Give evidence for a maximum tolerated dose, indicate toxic endpoints, e.g. deaths, clinical signs, etc., or state that no signs of toxicity were reported/observed.

Limit test

Enter 'Y' (Yes) or 'N' (No) only.

Route of administration

e.g. Oral, Dermal, or Inhalation, etc. In SNIF, only two characters are available for this entry, as follows:

	OR (oral)	DM (dermal)	IN (inhalation)
	IV (intra-venous)	IM (intra-muscular)	IP (intra-peritoneal)
	SU (sub-cutaneous)		

Vehicle	The vehicle should be described clearly and in full (not abbreviated). Also, state whether the test substance is in solution or suspension. SNIF permits up to 60 characters for this entry. e.g. Distilled water; 0.5% aqueous carboxymethylcellulose.
Observations	Free Text. Describe positive effects. Indicate if statistical significance or dose-response observed. In the case of negative results, provide a summary to confirm that control data are adequate. For-equivocal or positive results some details of the response observed should be given: e.g. type of structural damage, magnitude of effect, plus any dose response. Similar information is required if ploidy effects have been investigated.
Results	Only a single character entry ('+', '-', or '0') is permitted: (if equivocal '0', tick 'see comments' box). In cases where '0' is entered (equivocal), further explanation should be provided in the 'Comments' section. If ploidy effects have also been investigated, the overall result for this end-point should also be stated in the 'Observations' section.
with metabolic activation (+/-)	+
without metabolic activation (+/-)	-
Method (type of test)	Clearly indicate the source of the test-method protocol, e.g. 87/302/EEC or 92/69/EEC, OECD, or quoted publication, and the type of test, e.g. (Cytogenetics), (Micronucleus), (SCE), (UDS). It is preferred that approved test methods are used, if possible. However, other methods may be used when necessary provided they are well-validated and/or scientifically justified. Choice of test-method should have been made by discussion with the Competent Authority, and scientific justification included in the test report.
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	Free Text. Include any additional information here. If an overall negative result has been obtained it is necessary to comment on the adequacy of the test, e.g. provide justification for the dose levels used. In addition it should be remembered that a negative result in a bone marrow test in the absence of an effect on mitotic index or PIN ratio may occur due to failure of the test substance or its metabolites to reach the target tissue. In such a case the value of the result is limited.

4.3.34 *Rodent Dominant Lethal*

Limit test (YIN)

*Single character entry. Indicate **Y**(es) or **N**(o)*
Details of the dose used should be entered into the 'Comments' section, e.g.5000 mg/kg (single administration) or 1000 mg/kg (repeated administration).

Species/strain

Specify the species and (strain) of the test animal.
e.g. Rat (Wistar), Mouse (CD-1).

Route of administration

e.g. Oral, Dermal, or Inhalation, etc. In SNIF, only two characters are available for this entry, as follows:

OR (oral)	*DM (dermal)*	*IN (inhalation)*
IV (intra-venous)	*IM (intra-muscular)*	*IP (intra-peritoneal)*
SU (sub-cutaneous)		

Method of Administration or of exposure

State if single or repeated administration, and frequency.

Vehicle

The vehicle should be described clearly and in full (not abbreviated). Also, state whether the test substance is in solution or suspension. SNIF permits up to 60 characters for this entry erg. Distilled water; 0.5% aqueous carboxymethylcellulose.

Mass median aerodynamic diameter (for liquid an solid aerosols)

Free Text. Enter the size range, e.g. 2.2μ, or 75% of particles < 5μ.

Duration of exposure per day (inhalation or dermal) ... hours

Enter the daily exposure period as an integer

Dosing regime (5 or 7 days/week)

Enter '5' or '7' only.
Only a single numerical value is permissible here (5 or 7). If a single administration has been used, leave this field blank and enter details of the treatment in the 'Comments' section.

Results

Positive effects should be related to treatment and exposure level. If no sign of toxicity considered at 'tributable to the test substance is seen, this should be stated. Important effects should be described quantitatively as a deviation from the values seen in control animals.

Sex Dose/conc. (mg/kg), Number of animals, Group No

This is a Table, for Free Text entries. Unlimited number of lines permitted, e.g.

M	0	5	1
M	200	5	2
M	800	5	3

Effects seen in males	*Free Text. Describe any toxic effects observed during the period of the study.*
Number of pregnancies	*Free Text Indicate pregnancy rate for each dose group in order to assess affect of treatment*
Implantation effects	*Free Text Indicate pre- and post- implantation losses for each dose group.*
Overall result	*Free Text Indicate whether +ve or -ve dominant lethal effect.*
Method	*e.g. 87/302/EEC, B.22 (Dominant Lethal Assay)*
Body responsible for test	*Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.*
Comments	*Free Text Comment on the quality of the study. Describe the mating schedule. Refer to negative and positive control data. Include comments on the dosing regime.*

4.3.35 *Mouse Spot Test*

Species/strain	*Specify the species and (strain) of the test animal. Indicate both parental strains, e.g. T, HT; and include details of the genetic characteristics. This field is limited to 60 characters. If all of the relevant information cannot be entered here, provide further details in the 'Comments' section.*
Dose level (mg/kg)	*Units (mg/kg) are pre-defined in SNIF, therefore enter only numerical value. At least two dose levels should be used, and so it may be necessary to describe the dose levels in more detail in the 'Comments' section.*
Doses producing toxicity	*Free Text. Describe any toxic effects observed during the period of the study.*
Route of administration	*e.g. Oral, Dermal, or Inhalation, etc. In SNIF, only two characters are available for this entry, as follows:* *OR (oral) DM (dermal) IN (inhalation)* *IV (intra-venous) IM (intra-muscular) IP (intra-peritoneal)* *SU (sub-cutaneous)* *Normally single treatment, so indicate in 'Comments' section on which day this was administered, e.g. 8, 9 or 10.*
Vehicle	*The vehicle should be described clearly and in full (not abbreviated). Also, state whether the test substance is in solution or suspension. SNIF permits up to 60 characters for this entry.* *e.g. Distilled water; 0.5% aqueous carboxymethylcellulose.*
Observations	*Free text.*
Result	*Free text. Report all three classes of spots scored, i.e. WMVS, MDS, RS*
Method	*e.g. 87/302/EEC, B.24 (Mouse Spot Test).*

Body responsible for test *Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.*

Comments *Free Text. Comment on the quality of the study; strains used; dosing regime; and also on the use of negative and positive control data.*

4.3.36 *Mouse Heritable Translocation Test*

Species/strain *Mouse (specify the strain)*

Dose level (mg/kg) *Units (mg/kg) are pre-defined in SNIF, therefore enter only numerical value. Normally the Maximum Tolerated Dose would be used. However, if more dose levels are used they should be described in the 'Comments' section.*

Doses producing toxicity *Describe observations of toxic effect.*

Route of administration *e.g. Oral, Dermal, or Inhalation, etc. In SNIF, only two characters are available for this entry, as follows:*

OR (oral)	*DM (dermal)*	*IN (inhalation)*
IV (intra-venous)	*IM (intra-muscular)*	*IP (intra-peritoneal)*
SU (sub-cutaneous)		

Vehicle *The vehicle should be described clearly and in full (not abbreviated). Also, state whether the test substance is in solution or suspension. SNIF permits up to 60 characters for this entry. e.g. Distilled water, 0.5 % aqueous carboxymethylcellulose.*

Observations *Free text.*

Result *Free text. Indicate how heterozygosity was determined e.g.*
a) fertility testing of F_1 males, or
b) cytogenetic analysis of F_1 males.

Method *e.g. 87/302/EEC, B.25 (Mouse Heritable Translocation Assay).*

Body responsible for test *Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.*

Comments *Free Text. Comment on mean litter sizes obtained; number of F_1 offspring; whether F_1 male progeny only were assessed or both males and females; and on the use of negative and positive control data.*

4.3.37 *Sex Linked Recessive Lethal in Drosophila*

Species/strain *Indicate genotype of males, e.g. wild-type, and of females, e.g. Muller-5.*

Dose level (mg/kg) *Units (mg/kg) are pre-defined in SNIF, therefore enter only numerical value. Normally, three dose levels are used, and so it may be necessary to describe the dose levels in more detail in the 'Comments' section.*

Doses producing toxicity	*Describe in free text.*
Route of administration	*e.g. exposure to gas, vapour, etc., or dosed in diet.*
Vehicle	*The vehicle should be described clearly and in full (not abbreviated). Also, state whether the test substance is in solution or suspension. SNIF permits up to 60 characters for this entry. e.g. Distilled water, 0.5 % aqueous carboxymethylcellulose.*
Observations	*Free text.*
Result	*Indicate whether +ve or -ve mutagenic effect.*
Method	*e.g. 87/302/EEC, B.20 (Sex-linked Recessive Lethal Drosophila Assay)*
Body responsible for test	*Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.*
Comments:	*Free text. Comment on the quality of the study, and on the use of negative and positive control data.*

4.4.00 REPRODUCTION TOXICITY

The test methods in Annex V (currently in 87/302/EEC) should normally be used. However, when there is clear scientific justification, other methods may be used.

Nevertheless, it should be noted that the OECD reproductive toxicity screening tests (guidelines 421 and 422), which have been developed specifically for priority setting of existing chemicals, are **not** considered acceptable for classification of notified new substances.

For level 1 and level 2 the strategy for assessing the requirement for reproductive toxicity studies at higher supply levels is described in the Technical Guidance.

As indicated in the Technical Guidance Document, most regulatory authorities no longer require a three-generation study.

There is no EC or OECD test method for a developmental study on peri- and post-natal effects.

4.4.10 Reproductivity screening study (for the record)

4.4.20 *Reproductive Studies One Generation*

Limit test (Y/N)	*Single character entry. Indicate **Y**(es) or **N**(o).* *Details of the dose used should be entered into the 'Comments' section.*
Species/strain	*Specify the species and (strain) of the test animal.* *e.g. Rat (Wistar), Mouse (CD-1).*
Route of administration	*e.g. Oral, Dermal, or Inhalation, etc. In SNIF, only two characters are available for this entry, as follows:*

	OR (oral) *DM (dermal)* *IN (inhalation)* *IV (intra-venous)* *IM (intra-muscular)* *IP (intra-peritoneal)* *SU (sub-cutaneous)*
Method of administration or of exposure	*If oral, indicate whether by gavage or in diet/drinking water. If inhalation, indicate whether whole body or nose-only.*
Vehicle	*The vehicle should be described clearly and in full (not abbreviated). Also, state whether the test substance is in solution or suspension. SNIF permits up to 60 characters for this entry.* *e.g. Distilled water; 0.5% aqueous carboxymethylcellulose.*
Mass median aerodynamic diameter (for liquid and solid aerosols)	*Free Text. Enter the size range, erg. 2.2μ, or 75% of particles < 5μ.*
Duration of exposure per day (inhalation or dermal)...hours	*Enter the daily exposure period as an integer.*
Dosing Regime (5 or 7 days/week)	*Only a single integer ('5' or '7') is permitted here.*
Males days	*Give information about dosing/exposure period*
Females days	*e.g. for males, continual from 70 days prior to mating, for females, from 14 days prior to mating, through gestation and up to 21 days post-partum.*
Results	*Positive effects should be related to treatment and exposure level. If no sign of toxicity considered attributable to the test substance is seen, this should be stated. Important effects should be described quantitatively as a deviation from the values seen in control animals.*
Sex Dose/Conc. Number of animals Group No	*Provide this information in Table format. Unlimited number of lines is permitted. Units (mg/kg) are pre-defined in SNIF, so only numerical entries are permissible:*

M	0	20	1
M	10	20	2
M	100	20	3
M	1000	20	4
F	0	20	1
F	10	20	2
F	100	20	3
F	1000	20	4

Number of Litters per Dose/Conc.	*Report the number of litters produced at birth for each group. These are normally not standardised, e.g. to 8, thereafter.*
Dose level (mg/kg)	*Units (mg/kg) are pre-defined in SNIF, therefore enter only numerical value. Normally at least three dose levels should be used, and so it will be necessary to describe the dose levels in more detail in the 'Comments' section.*
Effects on parental animals	*The focus of attention for this study is on adverse effects on reproduction. The focus of attention for this section is on evidence of impaired reproductive ability in the parental animals.* *Report any signs of toxic effect which may have contributed to impairment of reproductive ability; deaths, adverse effect on body weight, food and water consumption, etc., and signs of ill-health throughout. Include observations of adverse effect seen at Necropsy.* *Comment on the behaviour of the dams during pregnancy and through the period of lactation.* *Comment on adverse effect, or no adverse effect, on reproductive performance, e.g. success in mating, pregnancy, parturition.*
Effects on F_1 generation	*The focus of attention for this section is on evidence of adverse effect on survival, growth and development of the offspring.* *Comment on adverse effect, or no adverse effect, on numbers at birth, and on survival and growth through lactation. Include comments on any adverse effect on body weight, or abnormal behavioural characteristics. Include observations of adverse effect seen at Necropsy, at weaning.*
Method	*e.g. 87/302/EEC, B.34 (single generation reproduction study)*
Body responsible for test	*Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.*
Comments	*Describe the mating schedule used.* *e.g. 1:1, producing F_1 or 1:2, producing F_1A and F_1B.* *If dosed in diet/drinking water, include here conversions from ppm to mg/kg.*

4.4.30 *Reproductive Studies Two or Three Generations*

Limit test (Y/N)	*Single character entry. Indicate **Y**(es) or **N**(o).* *Details of the dose used should be entered into the 'Comments' section.*
Species/strain	*Specify the species and (strain) of the test animal.* *e.g. Rat (Wistar), Mouse (CD-1).*
Route of administration	*e.g. Oral, Dermal, or Inhalation, etc. In SNIF, only two characters are available for this entry as follows:*

OR (oral) *DM (dermal)* *IN (inhalation)*
IV (intra-venous) *IM (intra-muscular)* *IP (intra-peritoneal)*
SU (sub-cutaneous)

The oral route is usually chosen, but other routes may have better justification.

Method of administration or of exposure

If oral, indicate whether by gavage or in diet/drinking water. If inhalation, indicate whether whole body or nose-only.

Vehicle

The vehicle should be described clearly and in full (not abbreviated). Also, state whether the test substance is in solution or suspension. SNIF permits up to 60 characters for this entry.
e.g. Distilled water; 0.5% aqueous carboxymethylcellulose.

Mass median aerodynamic diameter (for liquid and solid aerosols)

Free Text. Enter the size range, e.g. 2.2μ, or 75% of particles < 5μ.

Duration of exposure per day (inhalation or dermal)...hours

Enter the daily exposure period as an integer

Dosing Regime (5 or 7 days/week)

Only a single integer ('5' or'7') is permitted here.
Give below information about dosing/exposure period for each generation.
e.g. F_0, F_1 (or F_1A and F_1B), F_2 (or F_2A and F_2B), as appropriate:

Explain which generations were dosed/exposed, and for what period:

	Males days	**Females days**
F_0		
F_1		
F_2		

Sex Dose/Conc. Number of animals Group No

Provide this information in Table format, for each Generation of the study. Unlimited number of lines is permitted.

F_0 Generation
F_1 Generation
F_2 Generation

M	0	20	1
M	10	20	2
M	100	20	3
M	1000	20	4
F	0	20	1
F	10	20	2
F	100	20	3
F	1000	20	4

Number of litters per generation

Report the numbers at birth. Indicate in 'Comments' if litters were standardised, e.g. to 8, thereafter.

	Group 1	Group 2	Group 3	Group 4
F_1				
F_2				
F_3				

Results

Positive effects should be related to treatment and exposure level. If no sign of toxicity considered attributable to the test substance is seen, this should be stated. Important effects should be described quantitatively as a deviation from the values seen in control animals.

First Generation Stage

Effects on parental animals

The focus of attention for this study is on adverse effects on reproduction. The focus of attention for this section is on evidence of impaired reproductive ability in the parental animals.

Report any signs of toxic effect which may have contributed to impairment of reproductive ability; deaths, adverse effect on body weight, food and water consumption, etc., and signs of ill-health throughout. Include observations of adverse effect seen at Necropsy.

Comment on the behaviour of the dams during pregnancy and through the period of lactation.

Comment on adverse effect, or no adverse effect, on reproductive performance, e.g. success in mating, pregnancy, parturition.

Effects on F_1 generation

The focus of attention for this section is on evidence of adverse effect on survival,growth and development of the offspring. Specify if F_1A or F_1B.

Comment on adverse effect, or no adverse effect, on numbers at birth, and on survival and growth through lactation. Include comments on any adverse effect on body weight, or abnormal behavioural characteristics. Include observations of adverse effect seen at Necropsy, at weaning.

Second generation stage

Effects on parental animals (F_1 generation)

See first generation stage (for parents). Specify if F_1A or F_1B.

Effects on F_2 generation

See first generation stage (for offspring). Specify if F_2A or F_2B.

Third generation stage

Effects in parental animals (F_2 generation)

See first generation stage (for parents). Specify if F_2A or F_2B.

Effects on F_3 generation	See first generation stage (for offspring).
Method	e.g. 87/302/EEC, B.35 (two generation reproduction study).
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	Free Text. Comment on correlation of findings with preceding repeat-dose studies and/or preliminary dose-range-finding study for reproductive studies. If dosed in diet/drinking water, include here conversions from ppm to mg/kg.

4.4.40 Developmental Toxicity Teratogenecity

Limit test (Y/N)	*Single character entry. Indicate **Y**(es) or **N**(o)* *Details of the dose used should be entered into the 'Comments' section.*
Species/strain	*Specify the species and (strain) of the test animal.* *e.g. Rat (Sprague-Dawley); Rabbit (New Zealand White)*
Route of administration	*e.g. Oral, Dermal, or Inhalation, etc. In SNIF, only two characters are available for this entry, as follows:* *OR (oral)* *DM (dermal)* *IN (inhalation)* *IV (intra-venous)* *IM (intra-muscular)* *IP (intra-peritoneal)* *SU (sub-cutaneous)* The oral route is usually chosen, but other routes may have better justification.
Method of administration or of exposure	If oral, indicate whether by gavage or in diet/drinking water. If inhalation, indicate whether whole body or nose-only.
Vehicle	The vehicle should be described clearly and in full (not abbreviated). Also, state whether the test substance is in solution or suspension. SNIF permits up to 60 characters for this entry. e.g. Distilled water; 0.5% aqueous carboxymethylcellulose.
Mass median aerodynamic diameter, (for liquid and solid aerosols)	Free Text. Enter the size range, e.g. 2.2μ, or 75% of particles < 5μ.
Duration of exposure per day (inhalation or dermal)...hours	Enter the daily exposure period as an integer.

Dosing Regime (5 or 7 days/week)

Only a single integer ('5' or '7') is permitted here.
Give below information about dosing/exposure period for each generation,
e.g. F_0, F_1, (or F_1A and F_1B), F_2 (or F_2A and F_2B), as appropriate:

Number of dams, doses and group numbers

Units (mg/kg) are pre-defined in SNIF, therefore enter only numerical values for dose.

Dose or Conc. (mg/kg)	Number of Dams	Group No
e.g.		
0	15	1
5	15	2
25	15	3
125	15	4

Results in relation to dose levels/conc.

Positive effects should be related to treatment and exposure level. If no sign of toxicity considered attributable to the test substance is seen, this should be stated. Important effects should be described quantitatively as a deviation from the values seen in control animals.

Effects on Dam

Report deaths, effects on body weight, adverse effects on behaviour, and signs of ill-health.

Effects on foetus (Gross)

Report observations at Caesarian section, signs of abnormality, adverse effect on body weight, reduced size, etc.

Effects on foetus (Soft tissue)

Report observations from open dissection of foetuses (visceral examination) and/or from serial slices of fixed whole foetuses.

Effects on foetus (Skeletal)

Report observations from stained foetal skeletal preparations, or x-ray examinations.

Dose at which no toxic effects were observed:

Enter numerical data to indicate No Observed Adverse Effect Level, or, if this is not established, enter '<' lowest dose in study.

a) on dam **mg/kg/day, or mg/l/h/day**
b) on embryo/foetus **mg/kg/day, or mg/l/h/day**

Method

e.g. 87/302/ EC, B.31 (Developmental Toxicity Study)

Body responsible for test

Select the Testing Facility from the look-p list provided in SNIF, by entering the appropriate code.

Comments

Comment on method of insemination and pregnancy rate achievement in all groups. Consider signs of toxic effect in the dams when interpreting adverse effects in the foetus.

4.5.00 TOXICOKINETICS

4.5.10 Assessment of Toxicokinetic Behaviour

General

The assessment of the toxicokinetic behaviour of the substance is required to the extent that it can be made from evidence of all toxicological studies conducted and other relevant information to date on the test substance or its analogues. The aim is to consider all available information so that the most informed assessment about risk, and the need for further testing, can be made. It is a written assessment based on the base set data.

Include consideration of chemical structure, molecular weight, physical form, particle size, vapour pressure, water solubility, Log PoW, and information on hydrolysis. Evidence from structure activity relationships (SAR) and information about analogous structures may also provide useful information, i.e. what is known about absorption, distribution, metabolism and excretion of similar substances.

Observations of local and systemic effects in toxicity studies should be considered and differences in toxicity for routes other than those addressed in the base set studies. Consider also the potential for bioaccumulation and the influence of metabolic activation on the activity of the substances as observed in in-vitro mutagenicity assays.

4.5.20 *Toxicokinetic Study*

This index is used to summarise an experimental study of toxicokinetics.

Objective of the study	*Free Text Describe the purpose of the study.* *e.g. Absorption and distribution analysis, Identification of excreted metabolites.*
Test substance labelled (Y/N)	*Enter **Y**(es) or **N**(o).*
Details of label	*Free Text. Indicate the isotope used, the molecule that was labelled, e.g. test substance or a metabolite, and the position of the label.*
Species/strain	*Specify the species and (strain) of the test animal.* *e.g. Rat (Sprague-Dawley). Indicate if the animals were metabolically induced, e.g. with Aroctor.*
Route of administration	*e.g. Oral, Dermal, or Inhalation, etc. In SNIF, only two characters are available for this entry, as follows:* *OR (oral) DM (dermal) IN (inhalation)* *IV (intra-venous) IM (intra-muscular) IP (intra-peritoneal)* *SU (sub-cutaneous)* The oral route is usually chosen, but other routes may have better justification.

Method of administration and exposure

e.g. by gavage (oral), and indicate if single or repeated administration.

Vehicle

The vehicle should be described clearly and in full (not abbreviated). Also, state whether the test substance is in solution or suspension. SNIF permits up to 60 characters for this entry. e.g. Distilled water; 0.5 % aqueous carboxymethylcellulose.

Mass median aerodynamic diameter (for liquid and solid aerosols)

Free Text. Enter the size range, e.g. 2.2μ, or 75% of particles < 5μ.

Duration of exposure per day (inhalation or dermal)....hours

Enter the daily exposure period as an integer.

Dosing Regime (5 or 7 days/week)

Only a single integer ('5' or '7') is permitted here.
If the study involves only a single administration, leave this area blank.

Results

Enter the dose-group information in the Table below. Units (mg/kg) are pre-defined in SNIF, therefore enter only numerical values. If the dosing units are not mg/kg, describe the conversion in the 'Comments' section.

Sex	Dose/conc. (mg/kg)	Number of animals	Group No
M	100	5	1
M	1000	5	2
F	100	5	3
F	1000	5	4

Results

Free Text. Summarise the study clearly and concisely. Important aspects to consider are Site, timing, and frequency of sampling Tissues examined Half-lives for absorption and elimination Bio-availability Metabolites identified

However, do not interpret or discuss the results in this section. The discussion and conclusions should be in the 'Comments' section.

Method

If a published protocol is used, provide the reference here.

Body responsible for test

Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.

Comments

Free Text. Keep comments clear and concise. Enter details of the analytical methods used, e.g. LSC, GC, TLC, HPLC, etc. Include here discussion of the results and conclusion(s) of the study.

4.6.00 CHRONIC TOXICITY AND CARCINOGENICITY

The strategy for assessing the requirement for a Chronic Toxicity Study at higher supply levels is described in the Technical Guidance, as is the need to conduct a Carcinogenicity Study.

4.6.10 *Chronic Toxicity Test*

Species/strain	*Specify the species and (strain) of the test animal.* *e.g. Rat (Sprague-Dawley). The Rat is the preferred species. However data from studies using other species can be useful and should not be rejected.*
Dose or conc. at which no toxic effects were observed	*This is the dose or concentration at which no substance-related adverse effect of toxicological significance was observed. It should be noted that this dose level will usually be higher than that at which "No effect" is observed.*
mg/kg/day or, mg/1/…/h/day	*Enter value.* *If not established, give '<' lowest dose used in the study.*
Route of administration	*e.g. Oral, Dermal, or Inhalation, etc. In SNIF, only two characters are available for this entry as follows:* *OR (oral)* *DM (dermal)* *IN (inhalation)* *IV (intra-venous)* *IM (intra-muscular)* *IP (intra-peritoneal)* *SU (sub-cutaneous)*
Method of administration or of exposure	If oral, indicate whether by gavage or in diet/drinking water. If inhalation, indicate whether whole body or nose-only.
Vehicle	The vehicle should be described clearly and in full (not abbreviated). Also, state whether the test substance is in solution or suspension. SNIF permits up to 60 characters for this entry. e.g. Distilled water; 0.5 % aqueous carboxymethylcellulose.
Mass median aerodynamic diameter(for liquid and solid aerosols)	Free Text. Enter the size range, e.g. 2.2μ, or 75 % of particles < 5μ.
Duration of exposure per day (inhalation or dermal)...hours	Enter the daily exposure period as an integer.
Dosing Regime (5 or 7 days/week)	Only a single integer ('5' or '7') is permitted here.
Results	Positive effects should be related to treatment and exposure level. If no sign of toxicity considered attributable to the test substance is seen, this should be stated. Important effects should be described quantitatively as a deviation from the values seen in control animals.

	Sex Dose/conc. (mg/kg) Number of animals Group No **M** Enter the required numerical data in the Table **F**
Results (in relation to dose levels/ conc.)	Where appropriate, signs listed should be related to exposure level, time of onset, and duration. If no sign of toxicity considered attributable to the test substance is seen, this should be stated. Important effects should be described quantitatively as a deviation from the values seen in control animals.
1) Clinical observations	Free Text. Clear, concise and organised. Signs listed should be only those considered attributable to the test substance. Clinical observations include deaths, effects on body weight, food and water consumption, and any signs of ill-health.
2) Laboratory findings	As 1) above, covering haematology, blood chemistry and urinalysis values.
3) Effect in organs (general)	Summarise observations at necropsy (macroscopic) and at microscopic examination. It may be appropriate to distinguish effects seen in animals that died during the study (unscheduled) from those in animals killed as scheduled.
Effect in organs (tumours)	Provide a summary of masses observed at necropsy (macroscopic) and neoplasms identified after microscopic examination.
Dose or conc. at which no effect was observed	This is the dose or concentration at which no substance-related adverse effect was observed. It should be noted that this dose level will usually be lower than that at which "No toxic effect" is observed.
Mg/kg/day or, mg/l for...hours/day	If not established, give '<' lowest dose in this study.
Method	e.g. 87/302/EEC, B.30 (12 months Chronic Toxicity Study)
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	Free Text. Comment on the quality of the study, especially if conducted by he inhalation route. Report unusual circumstances which may have influenced the outcome of he study or the reliability of the results, e.g. intercurrent disease. If dosing was conducted in diet, or in drinking water, include here the calculated values for mean daily dosing, in mg/kg. Present the interpretation of results in order to justify the establishment of the No Observed Adverse Effect Level: e.g. It is not possible to establish a reliable and unequivocal no toxic effect level for this substance. e.g. As the effects observed at 100 and 1000 mg/kg were only minor, the dose at which no toxic effect occurred is considered to be 1000 mg/kg.

4.6.20 *Carcinogenicity Test*

The strategy for assessing the need to conduct a Carcinogenicity Study at higher supply levels is described in the Technical Guidance.

Species/strain	*Specify the species and (strain) of the test animal.* *e.g. Rat (Sprague-Dawley). The Rat is the preferred species. However data from studies using other species can be useful and should not be rejected.*
Dose or conc. at which no toxic effects were observed	*This is the dose or concentration at which no substance-related adverse effect of toxicological significance was observed. It should be noted that this dose level, which can indicate the need for R48, "Serious damage to, health" to be applied will usually be higher than that at which No, effect" is observed.*
Mg/kg/day or, Mg/l/…/h/day	*Enter value.* *If not established, give '<' lowest dose used in the study.*
Route of administration	e.g. Oral, Dermal, or Inhalation, etc. In SNIF, only two characters are available for this entry, as follows: OR (oral) DM (dermal) IN (inhalation) IV (intra-venous) IM (intra-muscular) IP (intra-peritoneal) SU (sub-cutaneous)
Method of administration or of exposure	If oral, indicate whether by gavage or in diet/drinking water. If inhalation, indicate whether whole body or nose-only.
Vehicle	The vehicle should be described clearly and in full (not abbreviated). Also, state whether the test substance is in solution or suspension. SNIF permits up to 60 characters for this entry. e.g. Distilled water; 0.5 % aqueous carboxymethylcellulose.
Mass median aerodynamic diameter (for liquid and solid aerosols)	Free Text. Enter the size range, e.g. 2.2μ, or 7 5% of particles < 5μ.
Duration of exposure per day (inhalation or dermal)...hours	Enter the daily exposure period as an integer
Dosing Regime (5 or 7 days/week)	Only a single integer ('5' or ‘7’) is permitted here.
Results	Positive effects should be related to treatment and exposure level. If no sign of toxicity considered attributable to the test substance is seen, this should be stated. Important effects should be described quantitatively as a deviation from the values seen in control animals.

	Sex Dose/conc. (mg/kg) Number of animals Group No **M** Enter the required numerical data in the Table **F**
1) Clinical observations	Free Text. Clear, concise and organised. Signs listed should be only those considered attributable to the test substance. Clinical observations include deaths, effects on body weight, food and water consumption, and any signs of ill-health.
2) Laboratory findings	As 1) above, covering haematology, blood chemistry and urinalysis values.
3) Effect in organs (general)	Summarise observations at necropsy (macroscopic) and at microscopic examination. It may be appropriate to distinguish effects seen in animals that died during the study (unscheduled) from those in animals killed as scheduled.
Effect in organs (tumours)	Provide a summary of masses observed at necropsy (macroscopic) and neoplasms identified after microscopic examination.
Dose or conc. at which no effect was observed	This is the dose or concentration at which no substance-related adverse effect was observed. It should be noted that this dose level will usually be lower than that at which "No toxic effect" is observed.
Mg/kg/day or, mg/l for...hours/day	If not established, give '<' lowest dose in this study.
Method	e.g. 87/302/EEC, 13.32 (Rat Carcinogenicity Study).
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	Free Text. Comment on the quality of the study, especially if conducted by the inhalation route. Report unusual circumstances which may have influenced the outcome of the study or the reliability of the results, e.g. intercurrent disease. If dosing was conducted in diet, or in drinking water, include here the calculated values for mean daily dosing, in mg/kg. Present the interpretation of results in order to justify the establishment of the No Observed Adverse Effect Level : e.g. It is not possible to establish a reliable and unequivocal no toxic effect level for this substance. e.g. As the effects observed at 100 and 1000 mg/kg were only minor, the dose at which no toxic effect occurred is considered to be 1000 mg/kg.

4.6.30 *Combined Chronic Toxicity/Carcinogenicity Test*

The strategy for assessing the need to conduct a Chronic/Carcinogenicity Study at higher supply levels is described in the Technical Guidance.

Species/strain	*Specify the species and (strain) of the test animal, e.g. Rat (F344). The Rat is the preferred species. However data from studies using other species can be useful and should not be rejected.*
Dose or conc. at which no toxic effects were observed	*This is the dose or concentration at which no substance-related adverse effect of toxicological significance was observed. It should be noted that this dose level, which can indicate the need for R48, "Serious damage to health" to be applied, will usually be higher than that at which "No effect" is observed.*
mg/kg/day or, mg/l/…/h/day	*Enter value.* *If not established, give '<' lowest dose used in the study.*
Route of administration	*e.g. Oral, Dermal, or Inhalation, etc. In SNIF, only two characters are available for this entry, as follows:* *OR (oral)* *DM (dermal)* *IN (inhalation)* *IV (intra-venous)* *IM (intra-muscular)* *IP (intra-peritoneal)* *SU (sub-cutaneous)*
Method of administration or of exposure	If oral, indicate whether by gavage or in diet/drinking water. If inhalation, indicate whether whole body or nose-only.
Vehicle	The vehicle should be described clearly and in full (not abbreviated). Also, state whether the test substance is in solution or suspension. SNIF permits up to 60 characters for this entry. e.g. Distilled water; 0.5% aqueous carboxymethylcellulose.
Mass median aerodynamic diameter(for liquid and solid aerosols)	Free Text. Enter the size range, e.g. 2.2μ, or 75% of particles < 5μ.
Duration of exposure per day (inhalation or dermal)...hours	Enter the daily exposure period as an integer.
Dosing Regime (5 or 7 days/week)	Only a single integer ('5' or '7' is permitted here.
Results	Positive effects should be related to treatment and exposure level. If no sign of toxicity considered attributable to the test substance is seen, this should be stated. Important effects should be described quantitatively as a deviation from the values seen in control animals.

	Sex Dose/conc. (mg/kg) Number of animals Group No **M** Enter the required numerical data in the Table **F**
Results (in relation to dose levels/ concentration)	Where appropriate, signs listed should be related to exposure level, time of onset, and duration. If no sign of toxicity considered attributable to the test substance is seen, this should be stated. Important effects should be described quantitatively as a deviation from the values seen in control animals.
1) Clinical observations	Free Text. Clear, concise and organised. Signs listed should be only those considered attributable to the test substance. Clinical observations include deaths, effects on body weight, food and water consumption, and any signs of ill-health.
2) Laboratory findings	As 1) above, covering haematology, blood chemistry and urinalysis values.
3) Effect in organs (general)	Summarise observations at necropsy (macroscopic) and at microscopic examination. It may be appropriate to distinguish effects seen in animals that died during the study (unscheduled) from those in animals killed as scheduled.
Effect in organs: (tumours)	Provide a summary of masses observed at necropsy (macroscopic) and neoplasms identified after microscopic examination.
Dose or conc. at which no effect was observed	This is the dose or concentration at which no substance-related adverse effect was observed. It should be noted that this dose level will usually be lower than that at which "No toxic effect" is observed.
mg/kg/day or, mg/l for...hours/day	If not established, give '<' lowest dose in this study.
Method	e.g. 87/302/EEC (Combined Chronic/Carcinogenicity Study).
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	Free Text. Comment on the quality of the study, especially if conducted by the inhalation route. Report unusual circumstances which may have influenced the outcome of the study or the reliability of the results, e.g. intercurrent disease. If dosing was conducted in diet, or in drinking water, include here the calculated values for mean daily dosing, in mg/kg. Present the interpretation of results in order to justify the establishment ofthe No Observed Adverse Effect Level: e.g. It is not possible to establish a reliable and unequivocal no toxic effect level for this substance.

e.g. As the effects observed at 100 and 1000 mg/kg were only minor, the dose at which no toxic effect occurred is considered to be 1000 mg/kg.

4.7.00 ADDITIONAL TOXICOLOGICAL STUDIES

General

These tests are not required for the reduced and base-set notifications (Annex VII A/B/C) but may be included voluntarily or they may, in certain circumstances, be requested by the Competent Authority immediately post base-set to clarify the results of the (reduced) base-set tests.

When the quantity of the substance supplied reaches the trigger points for supplementary notification (level 1 and level 2) the need for further toxicity tests should be considered.

If data on additional acute tests are to be included, then the results should be presented in the same format as for other acute tests (see sections 4.1.10, 4.1.20 and 4.1.30)

Tests for which no existing format should be given in this section.

End point investigated	e.g. Lymph node cell proliferation as an indication of skin sensitisation potential.
Description of the essential features of the test method	Include number, sex, and strain of mouse used, and details of the dosing regime.
Results	Indicate whether +ve or -ve response shown.
Test procedure used	e.g. Mouse Local Lymph Node Assay (Toxicology Methods, 1, 30-43 (1991).
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	Give summarised details of criteria for interpreting +ve response, e.g. est/control ratio for lymph node cell proliferative response > 3. If +ve result, indicate if labelling recommended, e.g. R43 If -ve result, comment if approved study, e.g. GPIVIT, will be requested. Comment on the use of negative and positive control data.

SECTION A5 ECOTOXICOLOGICAL STUDIES

5.1.00 EFFECTS ON ORGANISMS

General

Prior to conducting toxicity tests on aquatic organisms, it is important to obtain information on the solubility and the stability of the substance in the test medium, since these may differ from the result obtained under the water solubility test (see section 3.0.60).

A preliminary stability study will often be useful. If the loss of concentration over the test period is < 20%, either a static, semi-static, or flow-through exposure regime can be used. If the measured concentration drops by > 20%, a static system should not be used if suitable alternatives are available. If the loss of concentration over 24 hours is < 20% then, for the fish test, either a semi-static or a flow-through procedure can be used. If the loss of concentration is > 20% over 24 hours, a flow-through regime is recommended.

As required by Annex V, concentrations of test substance should be measured at least at the beginning and at the end of the test. In practice, it will normally be necessary to monitor this concentration more frequently. The LC_{50}'s, EC_{50}'s and NOEC's should be calculated based on the measured concentrations.

Where the measured concentrations are close to the nominal concentration, it is acceptable to calculate the LC_{50}'s, EC_{50}'s and NOEC's based on the nominal concentrations of the tested substance. In other cases, the geometric average measured concentration should be used.

A special case arises where substances decompose (hydrolyse, polymerize etc.) rapidly in the test media. When the DT50 < 4 hours a static test should be conducted to include the degradation products. When the DT50 > 12 hours, the parent substance should be studied using the appropriate exposure regime. When the DT50 falls between 4 and 12 hours, contact the Competent Authority to discuss the testing procedure.

For poorly soluble substances, it will not normally be necessary to conduct tests above the solubility limit in the test media. It may be useful, however, to conduct such tests in the presence of undissolved substance to ensure the maintenance of the exposure concentration during the test. Where possible, the test organisms should be physically separated from the undissolved fraction to avoid physical effects. Verification of the concentration of the dissolved substance should be made following centrification or filtration of the exposure media. The LC_{50}'s, EC_{50}'s and NOEC's should be calculated based on this dissolved concentration. Where no mortalities or effects are observed, the LC_{50}, EC_{50}, and NOEC should be recorded as being above the stated solubility limit.

Test methods for certain ecotoxicological properties are not yet included in Annex V. If national standard methods exist, then the additional information these tests provide for the purpose of assessment should be included in the notification.

5.1.01 Acute Toxicity for Fish

LC_{50}	The LC_{50} values should be given at 24, 48, 72 and 96h to evaluate the dose duration-effect relationship. All values quoted should be based upon actual and not nominal concentrations.
No-observed effect conc. (NOEC) at 96h	State the concentration without effect (physiological, behavioral etc.) at 96h. A NOEC might give an indication for delayed effects. An LC_0 is not the same as a NOEC and is not an acceptable substitute.
Species	Specify the species and (strain) of the test animal, e.g. Rainbow trout or Zebra-fish
Test	The type of test should be stated; single entry only 'ST' (static), 'SS' (semi static), or 'FT' (flow-through).
Loss in conc. of the test substance	Knowledge of any % loss in concentration during the test period is essential, especially for poorly water soluble substances since this will influence the calculation of the LC_{50} values.
Identity and conc. of auxiliary solvents	It is essential to have information on the auxiliary solvents and/or dispersion techniques used in the tests. If such devices are used it is necessary that appropriate "solvent" controls are also employed.
Water hardness	This information is necessary as for some substances the water hardness has a significant impact upon solubility and hence toxicity.
Dissolved oxygen conc. in water	The minimum concentration of oxygen in water should be at least 80 % of the air-saturation value. The oxygen concentration should be measured daily.
Method	e.g. Annex V, C. 1.
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	Comments should be made on any aspects of the test which may influence the results. Comments should be full but concise

5.1.02 Acute Toxicity for Daphnia

EC_{50}	The EC_{50} values should be given at 24 and 48h to evaluate the dose duration-effect relationship. All values quoted should be based upon actual and not nominal concentrations.
No-observed effect conc. (NOEC)at 48h	State the concentration without effect (physiological, behavioral etc.) at 48h. A NOEC might give an indication for delayed effects. An EC_0 is not the same as a NOEC and is not an acceptable substitute.
Species	Specify the species of the test animal; single entry only DM' (Daphnia magna) or 'DP' (Daphnia pulex).
Test	The type of test should be stated; single entry only 'ST' (static), 'SS' (semi static), or 'FT' (flow-through).

Loss in conc. of the test substance	Knowledge of any % loss in concentration during the test period is essential, especially for poorly water soluble substances since this will influence the calculation of the EC_{50} values.
Identity and conc. of auxiliary solvents	It is essential to have information on the auxiliary solvents and/or dispersion techniques used in the tests. If such devices are used it is necessary that appropriate "solvent" controls are also employed.
Water hardness	This information is necessary as for some substances the water hardness has a significant impact upon solubility and hence toxicity,
Dissolved oxygen conc. in water	The minimum concentration of oxygen in water should be at least 80 % of the air-saturation value. The oxygen concentration should be measured daily.
Method	e.g. Annex V, B.2.
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	Comments should be made on any aspects of the test which may influence the results. Comments should be full but concise.

5.1.03 Growth Inhibition Test on Algae

As for 5.1.01 above, except the as well as the NOEC for both endpoints should be submitted.

Limit test	Indicate with 'Y' (Yes) or 'N' (No) whether or not a limit test was performed.
EbC_{50} (Biomass) ErC_{50} (Growth)	The EC_{50} values of biomass (EbC_{50}) and relative growth (ErC_{50}) at 72 hour values should be given to evaluate the dose duration-effect relationship. All values quoted should be based upon actual and not nominal concentrations.
Duration of the test	Specify the duration of the test in hours; e.g.72.
Species	Specify the species of the test organism, e.g. Selenastrum capricomuturn, ATCC or Scenedesmus subspicatus SAG.
No-observed effect conc. for Growth and Biomass at 72h (NOEC)	State the concentration without effect (physiological, behavioural etc.) at 72h for growth and biomass. A NOEC(s) might give an indication for delayed effects. An EbC_0 and an ErC_0 are not the same as a NOEC and are not an acceptable substitute.
Type of test	The type of test should be stated; 'ST' (static), 'SS' (semi-static), or 'FT' (flow-through).
Loss in conc. of the test substance	Knowledge of any % loss in concentration during the test period is essential, especially for poorly water soluble substances since this will influence the calculation of the EC_{50} values.
Identity and conc. of auxiliary solvents	It is essential to have information on the auxiliary solvents and/or dispersion techniques used in the tests. If such devices are used it is necessary that appropriate "solvent" controls are also employed.

Water hardness	This information is necessary as for some substances the water hardness has a significant impact upon solubility and hence toxicity.
Dissolved oxygen conc. in water	The minimum concentration of oxygen in water should be at least 80 % of the air-saturation value. The oxygen concentration should be measured daily.
Method	e.g. 92/69/EEC, C.3 (Algal inhibition test)
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	Comments should be made on any aspects of the test which may influence the results. Comments should be full but concise

5.1.06 Inhibition of Microbial Activity

General

While this determination is not required for a reduced or base-set notification, it is nevertheless desirable to determine whether or not the test substance is toxic to bacteria. In those cases where biodegradation may be affected by the inhibitory effect of a substance on the bacteria, a test for bacterial inhibition should be carried out prior to undertaking the biodegradation. [if a high degree of toxicity is observed this will help in determining whether lack of degradation observed in the ready biodegradation is due to the recalcitrant properties of the test substance or to its toxicity.] Results obtained in this test for poorly water soluble substances should be interpreted with caution.

The IC_{50} and/or the NOEC should be reported, as well as the duration of the test.

5.1.07 *Long Term Toxicity to Daphnia Magna*

For the time being this test will have to be carried out to the OECD guideline 202 Part B. The whole procedure is currently being revised and awaits completion of an inter-laboratory calibration study, ring test, before it can be adopted.

EC_{50} (reproduction)	*This is to be based on actual concentrations wherever possible at 21 days.*
No-observed effect conc. NOEC	*State the concentration without effect (physiological, behavioural, etc) at 21 days.*
Type of Test	*Enter 'ST' (Static), 'SS' (Semi-Static) or 'FT' (Flow-Through). The present SNIF proforma does not allow to enter 'ST' for Static type, so use the 'Comment' section to provide the information.*
% Loss of test substance conc.	*It is essential to have information on loss since this must be taken into account in calculating the EC_{50} and NOEC values.*
Identity and conc. of auxiliary solvents	*These must be recorded together with any dispersion techniques used. If such devices are used then proper solvent controls must run in parallel with the test series.*

Water Hardness	*This must be determined and reported since it can have a significant effect on solubility and toxicity.*
Method	*e.g. OECD 202, Part B.*
Body responsible for test	*Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.*
Comments	*Comments should be made on any aspects of the test which have an influence on the results. Comments should be full but concise*

5.1.08 *Higher Plant Test*

Until such time as a revised protocol is available, the OECD Guideline 208 should be used. The test procedure is designed to study the effect of a substance on a higher plant if and when it can taken up through the root system. It does not apply to the study of effects of a substance taken up through the leaf system. It may be decided to test more than one species or strain of plant: a full summary is needed for each one tested.

Species/Strain	*Report the name of each species or strain tested.*
Duration of test	*Report the duration in days.*
Soil characteristics	*Report the types of each soil used. Report the pH, % organic matter, etc.*
EC_{50}	*Report the value for GROWTH in mg/kg at x days.*
LC_{50}	*Report the value for EMERGENCE in mg/kg at x days.*
No observed effect conc. (NOEC)	*Report the values of the NOEC at x days for GROWTH and EMERGENCE (mg/kg).*
Units used for recording values	*Report whether weights are on a dry or wet basis and length in mm.*
Phytotoxicity	*Record any signs noted and the nature, e.g. lack of colour.*
Method	*Report the method used; e.g. OECD 208.*
Body responsible for test	*Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.*
Comments	*Comments should be made on any aspects of the test which may influence the results. Comments should be full but concise.*

5.1.09 *Toxicity for Earthworms: Artificial Soil Test*

Species	*Report the species tested.*
Limit Test	*Enter 'Y' (Yes) or 'N' (No) only.*
Duration of the test	*Report the duration in days, normally 14.*
LC_{50}	*Report the value in mg/kg at x days, normally 14.*

Highest conc. without mortality	*Calculate the LC_0 value, mg/kg.*
Lowest conc. with 100% mortality	*Calculate the LC_{100} value, mg/kg.*
No observed effect conc. (NOEC)	*Report the NOEC value, mg/kg.* *Effects other than mortality, e.g. weight changes should be considered and reported in the "Comments" section.*
Soil characteristics	*Report the types of each soil used. Report the pH, % organic matter, etc.*
Method	*Report the method used.*
Body responsible for test	*Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.*
Comments	*Comments should be made on any aspects of the test which may influence the results. Comments should be full but concise.*

5.1.10 *Fish, Longer Term Toxicity Test (normally 14 days)*

This entry may include the results of not only the 14 day prolonged toxicity study but also those of studies on fish reproduction and early life stages.

<u>Prolonged Toxicity Study: 14 days or longer</u>

LC_{50}...days	*Report the value in mg/l.*
No observed effect conc. (NOEC)...days	*Report the value in mg/l.*
Lowest observed effect conc. (LOEC)...days	*Report the value in mg/l.*
Species	*Report the species tested.*
Type of test	*Enter 'ST' (Static), 'SS' (Semi-Static) or 'FT' (Flow-Through).*
Duration of Test	*Report the actual duration of the test and the unit of duration, e.g. 14 DYS (days).*
% loss in conc. of the test substance	*It is essential to have information on loss since this must be taken into account in the calculation of the LC_{50}, and NOEC values.*
Identity and conc. of auxiliary solvents	*These must be recorded together with any dispersion techniques used. If such devices are used then solvent controls must run in parallel with the test series.*
Water Hardness	*This must be determined and reported since it can have a significant effect on solubility and toxicity.*
Method	*Report the method used.*

Body responsible for test	*Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.*
Comments	*Comments should be made on any aspects of the test which may influence the results. Comments should be full but concise.*

Note

When a test has been carried out on the effect of a substance on Fish Early Life Stages, the parameter assessed e.g. embryo survival, time to hatch must be indicated. The NOEC and LOEC (Lowest Observed Effect Concentration) at x hrs in mg/l must be reported. The LOEC is not the same as LC_0 which is a calculated value for the highest concentration causing no mortality.

5.1.13 *Avian Oral Toxicity Test*

LC_{50}	*Report the value in mg/kg.*
Species	*Report the species used.*
Duration of the test	*Report the duration of the test x days.*
Dose at which no toxic effects were observed	*Report the value in mg/kg.*
Number of birds, doses and group numbers	*This is a Table, structured for entry of integers (number of birds), one text character (Sex), and numeric values (dose in mg/kg).*

Number of birds Male	***Dose mg/kg***	***Group Number***
		1
		2
		3
		4
		5

Number of birds Female	***Dose mg/kg***	***Group Number***
		1
		2
		3
		4
		5

Results (in relation to dose)	
1) Death	*Time of onset.*
2) Signs of toxicity	*Time of onset, duration, severity, incidence.*
Dose at which no effect observed	*Report the value in mg/kg.*
Method	*Report the method used.*

Body responsible for test	*Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.*
Comments	*Comments should be made on any aspects of the test which have an influence on the results. Comments should be full but concise.*

5.1.14 *Avian Reproduction Test*

Species	*Report the species used.*
Duration of feeding period of the test substance	*Report the period as x days.*
Dose levels of test substance used	*Report the dose used in mg/kg.*
Number of females	*Report the number used per dose.*
Dose at which no effects were observed	*Report the dose in mg/kg at x days.* *Report the parameters assessed e.g. egg production, egg viability, eggshell thickness.*
Results in relation to dose	*Report (1) Deaths, time of onset* *(2) Signs of toxicity, time of onset, duration, severity and incidence* *(3) Effects in organs.*
Method	Report the method used.
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code
Comments	Comments should be made on any aspects of the test which have a influence on the results. Comments should be full but concise.

5.2.00 DEGRADATION

General

An agreed strategy document XI/841/86-Final is available from the Competent Authority. In the case of slightly soluble substances, the method of dispersion, or the use of any carrier solvent, must be stated - including the name of the solvent and percentage used. In these cases the appropriate controls must be used. Where appropriate, further tests for inhibition of the activity of treatment organisms (see section 5.1.06), an "inherent" or "simulation" test may be carried out in addition to, or substituted for, the "ready test". For certain substances an anaerobic degradation test may be appropriate as an alternative, or in addition to, aerobic tests. In most cases the COD test alone, and its relationship with the COD value, is not sufficient to give an indication of the potential biodegrade.

5.2.11 Ready Biodegradability

General

The biodegradation curve should be drawn and in addition the experimentally determined values for the biodegradation experiment showing percentage degradation against time should be entered in the table. The biodegradation curve and experimental results should also be given for the reference substance. When poorly water soluble substances are tested, a description must be given of the nature and concentration, if appropriate, of any process and/or solvents used to enhance the contact between the substance and the microorganisms.

% degradation	Percentage degraded within 10-days of the start of degradation which point is taken as the time when 10% of the substance has been degraded (10-days time window).
Classification Readily biodegr.	For classification as readily biodegradable the following pass levels are recognized: tests based upon dissolved organic carbon >70% of theoretical maxima within a 10-days time window; tests based upon oxygen depletion or carbon dioxide generation >60% of theoretical maxima within the 10-days time window.
Reference substance	Give the name of the reference substance
Experimental values	Measured data for both the test substance and the reference substance should be given in the form of a table showing day of measurement/% degraded.
Degradation curve	Biodegradability in percentages against time in days
Method	Indicate specific test type.
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	Comments should be made on any aspects of the test which may influence the results. Comments should be full but concise. Record here the method of determination used, i.e. BOD/COD/DOC/specific.

5.2.12 Biochemical/Chemical Oxygen Demand (BOD/COD)

For guidance see section 5.2.11.

5.2.13 *Inherent Biodegradability*

Degradation	*Report as a %*
Inherent	*When the results indicate or not that the substance is inherently or partially biodegradable or eliminated, enter 'Y' (Yes) or 'N' (No).*
Duration of the test	*Report the duration of the test as x days.*
Reference substance	*Report the name of the substance if used.*
Initial test substance conc.	*Report the concentration stating clearly if mg/l of substances or mg/l DOC.*
Source of inoculum	*The origin of the inoculum must be reported.*
Experimental values	*The measured data should be reported in a table as follows:* ***Test substance*** ***Reference substance*** ***Day % removed*** ***Day % removed***
Degradation curve	*This must be supplied as a graph of time versus % degradability.*
Method	*This must be reported.*
Body responsible for test	*Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.*
Comments	*Comments should be made on any aspects of the test which may influence the results. Comments should be full but concise. Record here the method of determination used, i.e. BOD/COD/DOC/specific.*

5.2.14 Biodegradation in Wastewater Simulation Test

Removal	*Report as % with tolerance limit of 95% probability level and the respective standard deviation.*
Initial test substance conc.	*State this for the chosen analytical method(s) in mg17.*
Duration of test	*Report duration as x days.*
Mode of operation	*Indicate which mode used, i.e. single unit, coupled unit or non-coupled unit.*
Source of inoculum	*The origin of the inoculum must be stated.*
Sludge age	*This must be calculated and reported.*
Retention time	*This must be calculated and reported.*

Results	*The measured data should be reported in a table as follows:* ***Test substance Reference substance*** ***Day %removed Day % removed***
Method	*Report the method used, e.g. Annex V, C. 10.*
Body responsible for test	*Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.*
Comments	*Comments should be made on any aspects of the test which have an influence on the results. Include which method of determination was used, i.e. BOD/COD/DOC/ specific.*

5.2.15 Other Tests for Biodegradability/Elimination

This section should be used for reporting the results of anaerobic biodegradability/ elimination studies and also biodegradability/ elimination in soils and sediments. The end point investigated, a full description of the test procedure together with the results obtained should be given. The method used, the name and location of the test facility and concise relevant comments should be reported. It is recommended that the summary be based on one of the formats for biodegradation/ elimination if this is possible.

5.2.21 Hydrolysis as a Function of pH

General

This test need not be carried out if the substance is readily biodegradable or if the notifier can demonstrate, for example on the basis of chemical structure, that hydrolysis cannot be expected to play a significant role in the degradation of the substance in the environment. For poorly soluble substances (<1 mg/l), consideration may be given to omission of the test if it is not practical, i.e. the limit of detection of the analytical method does not allow quantification.

pH, T °C, K value/sec, t½ (hrs)

Method	Report the method used, e.g. 87/302/EEC C.7.
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	Comments should be made on any aspects of the test which have an influence on the results. Comments should be full but concise.

5.3.00 ADSORPTIONIDESORPTION

5.3.10 Adsorption/Desorption Screening Test

For base set notification (Annex VII A) determination of K_{oc} by HPLC analysis (Annex V test method C19) would normally be applicable. At upper tier notification (Annex VIII, levels 1 and

2) or in case of hazard concern, determination of adsorption/desorption on soils, including K_{oc}, using the batch equilibrium method (Annex V test method C18) would be applicable.

Where determination of K_{oc} at base set (method C19) is either technically not feasible or scientifically invalid, estimation of K_{oc} using QSAR prediction would be acceptable. QSAR calculations derive log K_{oc} from linear extrapolation of log K_{ow}. Either HPLC or batch equilibrium methods are valid for determination of K_{ow}. For many chemicals, HPLC analysis and QSAR estimation of K_{oc} would yield similar results.

K_{oc} values obtained from QSAR prediction are influenced according to alternative model equations, which should be applied as appropriate. Acceptable QSAR estimations also require conformity to validity criteria (e.g., non-polarised molecules, single functional group structures, etc.). In practice, the scope of QSAR prediction is limited to experienced case by case evaluation.

Further information is available from Commission technical guidance on risk assessment, respective of new (Directive 93/67/EEC) existing (Regulation 1488/94) and biocide (Directive 98/8/EC) substances (http://ecb.jrc.it/).

5.4.00 BIOACCUMULATION

5.4.10 *Bioconcentration Factor BCF*

Species	*Report the species used in the test.*
Type of test	*The type of test should be stated 'ST' (Static), 'SS' (Semi-Static) or 'FT' (Flow-Through).*
Concentration(s) of test substance	*Report the concentrations used in mg/l or mg/kg as appropriate.*
Duration of the test	*Report the duration in days.*
Method of calculation	*The applied calculation method should be stated 'SS' (Steady State) of K (Kinetic).*
of BCF	
Steady state	Concentration in organism in mg/kg after x days Uptake period, x days and no. of samples, y Depuration period, n days and no. of samples.
Kinetic	Uptake rate constant (K_1) in hr^{-1} Depuration rate constant (K_2) in hr^{-1} Depuration half life in days.
Bioconcentration Factor	
Whole body	State whether dry or wet weight basis.
Lipid	
Results	Tabulate the data used to calculate BCF

Steady state		**wet weight**	**dry weight**	**lipid tissue conc. wet weight**
	BCF whole body			
	BCF edible			
	BCF organ specific			

Kinetic method	Construct a similar table as for A Steady state.
% Loss in conc. in test period	It is essential to have information on loss so as to be able to estimate the exposure.
Identity and conc. of auxiliary solvents	These must be recorded together with any dispersion techniques used. If such devices are used proper solvent controls must be run in parallel with the test series.
Water hardness	This must determined and reported since it can have a significant effect on solubility and toxicity.
Test (solution) temperature and pH	These should be determined and reported.
Method	Report the method used.
Body responsible for test	Select the Testing Facility from the look-up list provided in SNIF, by entering the appropriate code.
Comments	Comments should be made on any aspects of the test which may have an influence on the results. Comments should be full but concise

5.5.00 ADDITIONAL ECOTOXICOLOGICAL TESTS

General

Any additional ecotoxicological tests should be reported here; e.g. bioconcentration factor and/or other accumulation data, photodegradation. Minimum information to be reported are: end point investigated; description of the essential features of the test method; results; test procedure used; body responsible for the test; comments.

The results of photodegradation studies and any other tests not covered in previous sections should be entered in this section. In all cases, it is recommended that wherever possible a format that can be adapted from those in earlier sections be used for reporting. When reporting additional toxicity studies on waste water treatment bacteria, the type of bacteria used must be specified, e.g. nitrifying or luminescent.

SECTION A6 POSSIBILITY OF RENDERING THE SUBSTANCE HARMLESS

6.1.00 FOR INDUSTRY/SKILLED TRADES

Indicate the general standard phrases and related codes to categorize the recommended possibilities for rendering the substance harmless and provide detailed technical information, if available. For standard phrases and codes see Annex 5 of this guidance.

6.1.10 Possibility of Recovery/Recycling of the Substance

Indicate possibilities for recycling of the used substance at normal use of the substance, quantities involved in spills and possibilities for recovery following spillage, and possibilities for collection of residues and/or contaminated substance and its container by the manufacturer or importer.

6.1.20 Possibility of Neutralisation (of any potentially hazardous effects).

Of particular importance to substances which are classified as hazardous. Possible chemical treatment(s) which will render the substance harmless should be indicated e.g. oxidation, hydrolysis, acid treatment, alkali-treatment, water-treatment, etc. If unknown, it should be justified. Comments made in section 2.3.10 should not be repeated in this section.

6.1.30 Possibility of Destruction

Controlled discharge	E.g. landfill, extensive dilution (to be specified) before discharge to surface water.
Incineration	Waste gas treatment should be indicated if necessary. Conditions for incineration of potential dioxin-producing compounds should be given.
Water purification system	Pre-treatment before discharge to sewage works should be mentioned as should recommended concentrations and any effects on the operation of the sewage works. Methods for recovery of the substance in order to prevent contamination of sewage works should also be given.
Others	

6.2.00 FOR THE PUBLIC AT LARGE

For guidance see notes under section 6.1.00.

6.2.10 Possibility of Recovery/Recycling

6.2.20 Possibility of Neutralisation (of any potentially hazardous effects)

6.2.30 Possibility of Destruction

Indicate how the public may dispose of the substance or preparations containing it.

Controlled discharge

Incineration

Water purification system

Others

SECTION A7 RISK ASSESSMENT

7.0.00 RISK ASSESSMENT

General

The risk assessment will be carried out by the Competent Authority. The notifier may submit on a voluntary basis a risk assessment of the notified substance. The risk assessment should be conducted according to the principles laid down in Directive 93/67/EEC. Supplementary detailed information helpful in carrying out a risk assessment are laid down in the technical guidance documents for new substances and for existing substances. Details on where to obtain the technical guidance documents are available from the Competent Authority.

The risk assessment should include the following information:

- hazard identification of the intrinsic hazardous properties of the substance (physico-chemical, toxicological and ecotoxicological properties);
- exposure assessment for the human population (i.e. workers, consumers and man exposed indirectly via the environment) and for the different environmental compartments likely to be exposed to the substance, based on levels derived from measured data or estimated using standardized scenarios;
- comparison of information on hazardous properties and exposure levels in order to characterise the degree of risk posed by the substance to human health or to the environment;
- integrated conclusions, separately for human health and the environment, including one or more of the type of conclusions set out in article 3 of Directive 93/67/EEC.

Guidance with regard to the format of the risk assessment (summary) report for notified substances is provided in document XI/133/94-Final available from the Competent Authority. Annex 1 of the document describes the format of the risk assessment report and Annex II give guidance how to complete the risk assessment report

SECTION B DECLARATION CONCERNING THE UNFAVOURABLE EFFECTS OF THE SUBSTANCE IN TERMS OF THE USES ENVISAGED

When a risk assessment has been provided this section can be omitted.

This declaration should be concise and is intended to take into account all potential dangers including those not covered or identified by the classification and labelling given under Section C. Indications for possible danger not tested so far should also be mentioned, e.g. indications for possible carcinogenic or mutagenic properties, for sensitisation by inhalation. All entries should be checked for consistency with the test results.

SECTION C PROPOSED CLASSIFICATION AND LABELLING

This section should include the classification and labelling proposed by the notifier; it should be consistent with the test results and with the rules and guidance for classification and labelling laid down in the Directive. Indicate in the classification all such markings as derived from the tests so far per-formed, including those which will not appear on the label due to the precedence rules. The classifications "carcinogenic", "mutagenic", and/or "toxic to reproduction" should be specified to the adequate category.

When the labelling of the marketed product differs from the proposed labelling of the substance itself because of difference in nature (e.g. in solution in stead of pulverized), specify also the labelling of the substance in marketed condition.

Not fully tested substances (submitted with a reduced notification) should bear, in addition to the label deriving from the tests already carried out, the warning: "Caution - substance not yet fully tested".

SECTION D PROPOSALS FOR ANY RECOMMENDED PRECAUTIONS RELATING TO THE SAFE USE OF THE SUBSTANCE; PROPOSED SAFETY DATA SHEET

For dangerous substances only, include a safety data sheet in accordance with Directive 91/155/EEC. Attach as an annex, do not enter additional text or data in this section.

To enable professional users in particular to take the necessary measures as regards the protection of the environment and health and safety at the workplace. Before the first delivery of a dangerous substance, any manufacturer, importer or distributor shall communicate to the recipients this safety data sheet. The sheet should contain the information necessary for protection of man and the environment. All information in the safety data sheet should be checked for consistency with the test results reported in the summary.

Although not required, it is recommended to submit also a safety data sheet for non-dangerous substances.

ANNEX 1 EXPLANATORY NOTE WITH REGARD TO THE SECTIONS OF ANNEX VII TO COMPLETE FOR A (REDUCED) NOTIFICATION

Depending on the quantity of the substance marketed in the EEA the following information should be provided and the relating sections to be filled in.

1 A notification according to Annex VII A: Base set dossier (> 1000 kg/year/notifier):

Section 0, Al, A2, A3, A4, A5, A6, B, C, D, E.

Sections A4.4 10 and A5.3. 10 of the summary form are at this moment for the record. Any already available information about the reproductive toxicity and adsorption/desorption must be reported in these sections.

2 A notification according to Annex VII B: reduced base set notification (100-1000 kg/year/manufacturer):

Sections 0, Al, A2, A6, B, C, D, E.
From sections A3, A4 and A5 at least the following tests:
A3.0.00, A3.0.10, A3.0.20, A3.0.60, A3.0.80, A3.0.90, A3.1.00
A4. 1. 10 (or A4.1.20), A4.1.50, A4.1.60, A4.1.70, A4.3. 10
A5.2.11

Depending on national provisions also information on vapour pressure (section A3.0.40) and/or acute Daphnia toxicity (section A5.1.02) might be requested at this level.

3 A notification according to Annex VII C: reduced base set notification (10-100 kg/year/manufacturer):

Sections 0, Al, A2, A6, B, C, D, E.
From sections A3 and A4 at least the following tests:
A3.0.00, A3.0.90, A3.1.00 A4. 1. 10 (or A4.1.20).

4 Polymers (Annex VII D)

Directive 93/105/EEC contains a specific test strategy for polymers. In addition to the test package, in analogy to Annex II of Directive 67/548/EEC, it comprises a concept for grouping polymers into families of polymers (family approach) and provides a reduced test package for polymers fulfilling specific criteria. A guidance document on the notification of polymers (currently XI/584/93 rev. 2) is available from the Competent Authority.

C.1 Polymers with standard test package

C.1.1 Annex VII D, C.1.1, base set for polymers (> 1000 kg/year/manufacturer):

In addition to the information and test referred to in Annex VII A, the following polymer-specific information is required:

From sections Al, A2 and A3 the following tests:
A1.3.10.120, A1.3.10.130, A1.3.30, A1.3.32, A1.3.33
A2.1.35
A3.1.60

C.1.2 Annex VII D, C.1.2 reduced base set for polymers (100-1000 kg/year/manufacturer):

In addition to the information and test referred to in Annex VII B, the following polymer-specific information is required:

From sections Al, A2 and A3 the following tests:
A1.3.10.120, A1.3.10.130, A1.3.30, A1.3.32, A1.3.33
A2.1.35 A3.1.60.

C.1.3 Annex VII D, C.1.3 reduced base set for polymers (10-100 kg/year/manufacturer):

In addition to the information and test referred to in Annex VII C, the following polymer-specific information is required:

From sections A1 and A2 the following tests:
A1.3.10.120, A1.3.10.130, A1.3.30, A1.3.32, A1.3.33
A2.1.35

C.2 Polymers for which a reduced test package is acceptable

Under certain conditions the base set test package for polymers can be reduced. Substances with a high number-average molecular weight, a low content of low molecular weight species and a low solubility/extractivity will be regarded as being non-bioavailable.

Consequently, the following criteria shall be used to determine the polymers for which a reduced test package is acceptable:

1. High number-average molecular weight (Mn);

2. Extractivity/Solubility in water (A.3.0.60)
   < 10 mg/l excluding any contribution from additives and impurities;

3. Less than 1% with M <1000: the percentage refers only to molecules (components) directly derived from and including monomer(s), excluding other components e.g. additives or impurities; if all criteria are fulfilled, the polymer is regarded as polymer for which a reduced test package is acceptable. In the case of polymers placed on the Community market in amounts <1000 kg/year/manufacturer or total quantities of <5000 kg it is sufficient that criteria 1 and 2 are fulfilled for the polymer to be considered a polymer for which a reduced test package is acceptable. If it is not possible to prove the

criteria with the assigned tests, the notifier has to demonstrate compliance with the criteria by other means.

C.2.1 Annex VII D, C.2.1 (RTP) (> 1000 kg/year/manufacturer):

Sections 0, Al, A2, A6, B, C, D, E
From section A3 the following tests:
A.3.0.00, A.3.0.10, A.3.0.30, A.3.0.60, A.3.1.00, A.3.1.10, A.3.1.20, A.3.1.50, A.3.1.60

Section A4:

On a case by case basis, some tests may be required by the Chemical Substance Bureau, without delaying the acceptance of the notification, depending on the presence of reactive groups, structural/physical characteristics or knowledge of the properties of low molecular components of the polymer or exposure potential, namely tests for inhalation toxicity if a potential of such exposure exists.

Section A5:

On a case by case basis, some tests may be required by the Chemical Substance Bureau, without delaying the acceptance of the notification, depending on the presence of reactive groups, structural/physical characteristics or knowledge of the properties of low molecular components of the polymer or exposure potential.

The following additional tests may be required in certain cases:

light-stability, if the polymer is not specifically light-stabilized

long-term extractivity (leachate test)

Depending on the results of this test, any other appropriate test on the leachate may be requested on a case by case basis.

C.2.2 Annex VII D, C.2.2 (RTP) (10-1000 kg/year/manufacturer):

Sections 0, A1, A2, A6, B, C, D, E
From section A3 the following tests:
A.3.0.00, A.3.0.10, A.3.0.60, A.3.1.00

ANNEX 2 INDUSTRIAL CATEGORY: INDUSTRY IN WHICH THE SUBSTANCE IS USED

1 Agricultural industry
e.g. Plant protection products; fertilisers.

2 Chemical industry: basic chemicals
e.g. Solvents; pH-regulating agents (acids, alkalis).

3 Chemical industry: chemicals used in synthesis
e.g. Intermediates (including monomers); process regulators.

4 Electrical/electronic engineering industry
e.g. Electrolytes; semiconductors.
Not galvanics; electroplating agents.

5 Personal/domestic
e.g. Consumer products such as detergents (including additives); cosmetics; non-agricultural biocides for domestic use.

6 Public domain
e.g. Professional products used in public areas such as non-agricultural biocides, cleaning agents; office and office machinery products such as correction fluids, printing inks.

7 Leather processing industry
e.g. Dyestuffs; tanning auxiliaries.

8 Metal extraction refining and processing industry
e.g. Heat transferring agents; electroplating agents.

9 Mineral oil and fuel industry
e.g. Gasoline; motor oil; gear oil; hydraulic fluid; colouring agents; fuel additives; antiknock agents; waste oil detoxification agents.

10 Photographic industry
e.g. Antifogging agents; sensitisers.

11 Polymers industry
e.g. Stabilisers; softeners; antistatic agents; dyestuffs.

12 Pulp, Paper and board industry
e.g. Dyestuffs; toners.

13 Textile processing industry
e.g. Dyestuffs; flame retardants.

14 Paints, lacquers and varnishes industry
e.g. Solvents; viscosity adjustors; dyestuffs; pigments.

15 Engineering industry: civil and mechanical
e.g. Agents used in construction work; agents used in automobile, aircraft and ship building.

999 Other

Note:

The function category 'Others', previously numbered 0 (zero), is now numbered 999. The number 0 is no longer used and will not be reassigned.

ANNEX 3 FUNCTION CATEGORIES

1 Absorbents and adsorbents
Materials used to absorb or adsorb gases or liquids: filter materials/media; molecular sieves; silica gel etc

2 Adhesives, binding agents
Materials which are applied to two surfaces causing them to adhere: dispersion-based adhesives; hotmelt; resins for polymer-based hardening adhesives; solvent based adhesives.

3 Aerosol propellants
Compressed or liquefied gases within which substances are dissolved or suspended and expelled from a container upon discharge of the internal pressure through expansion of the gas.

4 Anti-condensation agents
Substances used to avoid condensation on surfaces and in the atmosphere: anti-dim agents; condensation removers.

5 Anti-freezing agents
Substances used to prevent and remove ice formation: antifreeze liquids; de-icing agents.

6 Anti-set-off anti-adhesive agents
Substances used to prevent set-off and adhesion: spraying powder and anti-set-off additives for printing; oils and waxes for laths and shuttering; casting slip etc

7 Anti-static agents
Substances used to prevent or reduce the tendency to accumulate electrostatic charges: anti-static additives; substances for surface treatment against static electricity.

8 Bleaching agents
Substances used to whiten or decolourise materials.
Not: cosmetics; photographic bleaches; optical brighteners.

9 Cleaning/washing agents and additives
Substances used to remove dirt or impurities from surfaces.
Sub-categories: detergents; soaps; dry cleaning solvents; optical brighteners in detergents.

10 Colouring agents
Substances used to impart their colour to other materials.
Sub-categories: dyestuffs; pigments (including toners); colour forming agents; fluorescent brighteners (but see below re detergents).
Not: cosmetics; food colours; photo-chemicals; optical brighteners used exclusively in detergents; reprographic agents.

11 Complexing agents
Substances used to combine with other substances (mainly metal ions) to form complexes.

12 Conductive agents
Materials used to conduct electrical current.
Sub-categories electrolytes; electrode materials.

13 Construction materials and additives
Substances used in building materials and constructional articles: wall construction materials; road surface materials; ceramic, metal, plastic and wooden construction materials.

14 Corrosion inhibitors
Substances used to prevent corrosion: corrosion inhibiting additives; rust preventives.

15 Cosmetics
Substances used as components of cosmetic and toiletry formulations

16 Dust binding agents
Substances used to control finely divided solid particles of powdered or ground materials to reduce their discharge into the air.

17 Electroplating agents
Substances used as a source for a layer of metal deposited on another surface; or that aid such a deposition.

18 Explosives
Substances or mixtures that are characterised by chemical stability but that may be made to undergo chemical change, rapidly producing a large quantity of energy and gas accompanied by bursting or expansion.
Sub-categories: blasting agents; detonators; incendiaries.

19 Fertilisers
Substances used to supply chemical elements needed for plant nutrition.

20 Fillers
Relatively inert, and normally non-fibrous, finely divided substances added to elastomers, plastics, paints, ceramics etc., usually to extend volume which may improve desired properties such as whiteness, lubricity, density or tensile strength.

21 Fixing agents
Substances used to interact with a dye on fibres to improve fastness.

22 Flame retardants and fire preventing agents
Substances incorporated into, or applied to the surface of, materials to slow down or prevent combustion.

23 Flotation agents
Substances used to concentrate and obtain minerals from ores: flotation oil; flotation depressants.

24 Flux agents for casting
Substances used to promote the fusing of minerals or prevent oxide formation.

25 Foaming agents
Substances used to form a foam or cellular structure in a plastic or rubber material: physically by expansion of compressed gases or vaporisation of liquid, or chemically by decomposition evolving a gas.
Sub-categories: chemical or physical blowing agents; frothers.

26 Food/feedstuff additives
Substances used in food or animal feedstuffs to produce or enhance taste, odour or colour or to improve conservation.

27 Fuels
Substances used to evolve energy in a controlled combustion reaction
Sub-categories: gasoline; kerosine; gas oil; fuel oil; petroleum gas; non-mineral oil.

28 Fuel additives
Substances added to fuels.
Sub-categories: anti-fouling agents; antiknock agents; deposit modifiers; fuel oxidizers.

29 Heat transferring agents
Substances used to transmit or to remove heat from a material.
Sub-categories cooling agents; heating agents.

30 Hydraulic fluids and additives
Fluids used for transmitting pressure.

31 Impregnation agents
Substances used to admix with solid materials, which retain their original form: impregnating agents for leather, paper, textile and wood.
Not: flame retardants; conserving agents; biocides.

32 Insulating materials
Agents used to prevent or inhibit the flow of electrical current, heat or light or the transmission of sound.

33 Intermediates
Substances used for synthesis of other chemicals.
Sub-categories: monomers; pre-polymers.

34 Laboratory chemicals
Substances used in laboratories for analytical purposes.

35 Lubricants and additives
Substances entrained between two surfaces and thereby used to reduce friction: oils; fats; waxes; friction reducing additives.

36 Odour agents
Substances used to produce, enhance or mask odour.
Not: food additives; cosmetics.

37 Oxidizing agents
Substances that give up oxygen easily, remove hydrogen from other substances, or accept electrons in chemical reactions, and are used for such purposes.

38 Plant protection Products. agricultural
Active ingredients and preparations containing one or more active ingredients, intended to protect plants or plant products against harmful organisms or prevent the action of such organisms, influence the life processes of plants, preserve plant products, destroy undesirable plants or destroy parts of plants.
Not: nutrients; fertilisers.

39 Biocides non-agricultural

Active substances and preparations containing one or more active substances, intended to destroy, deter, render harmless, prevent the action of or otherwise exert a controlling effect on any organism which has an unwanted presence for man, or a detrimental effect for man, his activities or the products he uses or produces; or for animals or for the environment.
Sub-categories: disinfectants, preservative products, pest control products, specialist biocides.
Not: plant protection products; veterinary products.

40 pH-regulation agents

Substances used to alter or stabilise the hydrogen ion concentration (pH): acids; alkalis; buffers.

41 Pharmaceuticals

Substances used as active ingredients in medicinal preparations.
Sub-category: veterinary medicines.

42 Photochemicals

Substances used to create a permanent photographic image.
Sub-categories: desensitisers; developers; fixing agents; photosensitive agents; sensitisers; anti-fogging agents; light stabilisers; intensifiers.

43 Process regulators

Substances used to regulate the speed of a (chemical) process.
Sub-categories: accelerators; activators; catalysts; inhibitors; siccatives; anti-siccatives; Cross-linking agents; initiators; photo-initiators etc

44 Reducing agents

Substances used to remove oxygen, hydrogenate or, in general, act as electron donors in chemical reactions.

45 Reprographic agents

Substances used to reproduce a permanent image.
Sub-categories: toner for photocopying machines; toner additives.

46 Semiconductors

Substances having resistivities that are between those of insulators and metals, and are usually changeable by light, heat or electrical or magnetic field, or generate electromotive force upon the incidence of radiant energy.
Sub-categories: semiconductors; photovoltaic agents.

47 Softeners

Substances used for softening materials to improve feel, to facilitate finishing processes or to impart flexibility or workability.
Sub-categories: coalescing agents; bates (leather technology); devulcanising agents; emollients; swelling agents; water softeners; plasticisers

48 Solvents

Substances used to dissolve, thin, dilute and extract: extraction agents; solvents and thinners for paints, lacquers, adhesives and other materials.

49 Stabilisers
Substances used to prevent or slow down spontaneous changes in, and aging of, materials.
Sub-categories: antioxidants; heat stabilisers; light stabilisers; scavengers; charge stabilisers.

50 Surface-active agents
Substances used to lower the surface and/or interfacial tension of liquids and promote cleaning, wetting, dispersion etc

51 Tanning agents
Substances used for treating hides and skins.

52 Viscosity adjustors
Substances used to modify the flow characteristics of other substances, or mixtures, to which they are added.
Sub-categories: pour point depressants; thickeners; thixotropic agents; turbulence supressors; viscosity index improvers.

53 Vulcanising agents
Substances added to rubber to aid and hasten vulcanisation: vulcanising accelerators and vulcanising assistants.

54 Welding and soldering agents
Materials used for welding and soldering; electrodes; flux; powdered metal; wire etc..

999 Others
Substances whose technical functions are not described elsewhere.

Note:
The function category 'Others', previously numbered 0 (zero), is now numbered 999. The number 0 is no longer used and will not be reassigned.

ANNEX 4 EXAMPLES ILLUSTRATING THE USE OF THE INDUSTRIAL (ANNEX 1) AND FUNCTION (ANNEX 3) CATEGORIES

1. Dyestuff for artificial fibres/fabrics Use category: Annex I category 13 (Textile processing industry).

Desired effects: Annex II category 10 (Colouring agents; sub-category: dyestuffs). 'Detailed information' should include an outline of the formulation and dyeing processes, degree of fixation etc., as appropriate.

2. Hair conditioner

Use category:
Annex I category 5 (Personal/domestic).

Desired effects:
Annex II category 15 (Cosmetics).

3. Pesticide intermediate

Use category:
Annex I category 3 (Chemical industry: chemicals used in synthesis).

Desired effects:
Annex II category 33 (Intermediates). 'Detailed information' should include an outline of the process; frequency and duration of synthesis.

4. Fungicide for cereal crops

Use category:
Annex I category 1 (Agricultural industry).

Desired effects:
Annex II category 38 (Plant protection products, agricultural). 'Detailed information' should include information on target and/or protected species; mode and frequency of application. Formulation data - type, how prepared etc. - would also be useful.

5. Disinfectant

Use categories:
Annex I category 1 (Agricultural industry). 20%
Annex I category 5 (Personal/domestic). 5%
Annex I category 6 (Public domain). 75%

Desired effects:
Annex II category 39 (Biocides, non-agricultural; sub-category: disinfectants). 'Detailed information' should include information on mode and frequency of use.

6. Blasting agent (explosive)

Use category:
Annex I category 999 (Others: stone quarrying industry).

Desired effects:
Annex II category 18 (Explosives; sub-category: blasting agents).

7. Additive: flame retardant for polyurethane foams and polyester textiles

Use categories:

Annex I category 11 (Polymers industry).
Annex I category 13 (Textile processing industry).

Desired effects:
Annex II category 22 (Flame retardants and fire preventing agents).

8. Additive to photocopier toner

Use categories:
Annex I category 6 (Public domain).
Annex I category 12 (Pulp, paper and board industry).

Desired effects:
Annex II category 45 (reprographic agents; sub-category: toner additives).

9. Inert liquid with multiple uses

Use categories:
Annex I category 2 (Chemical industry: basic chemicals). 15%
Annex I category 4 (Electrical/electronic engineering industry). 80%
Annex I category 999 (Other: medical diagnostics). 5%

Desired effects:
Annex II category 29 (Heat transferring agents).
Annex II category 999 (Other:
a. test liquid in electronic industry;
b. separation of liquids during transport or analysis).

ANNEX 5 CATEGORIES OF RECOMMENDED MEASURES FOR RENDERINGTHE SUBSTANCE HARMLESS PROVIDED IN SECTION 6

A: Methods for substances used by the industry
B: Methods for substances used by the public
C: Both

Recovery

[610	Recovery, not specified]
611	Recovery by mechanical collection
612	Recovery by recycling
613	Recovery by chemical purification
614	Recovery by distillation
615	Recovery by sublimation
616	Recovery by evaporisation
617	Recovery by dehydration [1 condensation]
618	Recovery by extraction
619	Recovery by adsorption
620	Recovery by absorption
621	Recovery by precipitation followed by filtration
622	Recovery by filtration
622	Recovery by solid/liquid separation
623	Recovery by special techniques (notifier to specify)

Neutralisation

[630	Neutralisation, not specified]
631	Neutralisation by acid-treatment
632	Neutralisation by alkali-treatment
633	Neutralisation by water treatment
634	Neutralisation by special techniques (notifier to specify, e.g. in an installation for detoxification/ neutralisation/ dehydration/ sedimentation/ oxidation)

Removal in treatment plants

[640	Removal, not specified]
641	Removal by controlled discharge to a wastewater treatment plant (notifier to specify conditions)
642	Removal by aerobic treatment
643	Removal by anaerobic treatment

Landfill

650	Removal by controlled dumping at a licensed landfill

Destruction by incinerate

[660	Incinerate, not specified]
661	Incinerator with flue gas scrubbing
662	Incinerate, high temperature-long burn (*)
663	Incinerate, high temperature-long burn (*) with flue gas scrubbing

664 Incinerate in halogen specific incinerator

665 Incinerate in other specific incinerators (notifier to specify) (*) minimum temperature of 1200 °C, at least 2 seconds' residence time, excess oxygen

Other destructive techniques

671 Pyrolysis

672 Destructive distillation

673 Destruction by hydrolysis

ANNEX 6 INFORMATION THAT MAY BE REQUIRED FOR A REQUEST FOR A PROCESSORIENTATED RESEARCH AND DEVELOPMENT EXEMPTION

The following points should be addressed by the applicant, where applicable:

1. a) What is the chemical identity of the substance i.e. structure, IUPAC name, CAS number, impurities, essential additives, spectral data etc?

   b) What is the envisaged use of the substance?

   c) What R & D work has already been carried out either by yourself or, if appropriate, by the customers involved in the R & D programme (e.g. internally or under the <100kg per annum scientific R & D exemption)?

2. a) What is your justification for wanting to use this exemption (including an assurance that you do not currently know whether you can achieve the desired effect and that you need to carry out research and development to do so)?

   b) What additional information will be gained through the proposed R & D programme? What other methods have been considered for obtaining this information?

   c) Please give a summary of the R & D plan, including the process to be investigated, the timetable and a proposed start date.

   d) Which parameters will be investigated?

   e) What is the justification for the quantity involved in the proposed R & D programme (including justification for the number of batches and quantity per batch etc)?

3. a) What is the name and address of the manufacturer of the substance (if not the applicant)?

   b) Which customers will receive the substance and why and how much will each customer receive (please provide names, addresses and contact names)?

4. a) Have you made an application to any other Member States? If so please provide details including the status of these applications.

Either at the time you write requesting an exemption or once we are satisfied with your justification and grant an exemption please provide:

5. a) confirmation that the substance, or any preparation containing it, will only be handled by the customers staff under controlled conditions and will not be made available to the general public;

6. a) information on how customer(s) ensure protection of people and the environment (e.g. by the provision of an adequate label-including the phrase "Caution-substance not yet fully tested"-disposal procedures etc);

7. a) any test data that is already available on the substance (final results only);

   b) details of any tests you intend to carry out;

8. a) estimated date of the corresponding notification; and

9. a) information on whether you intend to use the substance to produce articles and whether these would be made available to the general public.

The mission of the JRC is to provide customer-driven scientific and technical support for the conception, development, implementation and monitoring of EU policies. As a service of the European Commission, the JRC functions as a reference centre of science and technology for the Union. Close to the policy-making process, it serves the common interest of the Member States, while being independent of special interests, private or national.

EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

European Commission – Joint Research Centre
Institute for Health and Consumer Protection
European Chemicals Bureau (ECB)

NOTIFICATION OF NEW CHEMICALS SUBSTANCES IN ACCORDANCE WITH DIRECTIVE 67/548/EEC ON THE CLASSIFICATION, PACKAGING AND LABELLING OF DANGEROUS SUBSTANCES